UNITED STATES
SECURITIES AND EXCHANGE COMMISSION

Washington, D.C. 20549

FORM 10-K

(Mark One)

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

For the fiscal year ended December 31, 2018

OR

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

For the transition period from _____ to _____

Commission File No. 001-38359

resTORbio, Inc.

(Exact name of registrant as specified in its charter)

Delaware	**81-3305277**
(State or other jurisdiction of incorporation or organization)	**(I.R.S. Employer Identification No.)**

500 Boylston Street, 12th Floor
Boston, MA 02116
(857) 315-5521

(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	**Name of each exchange on which registered**
Common Stock, par value $0.0001 per share	**Nasdaq Global Select Market**

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

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

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

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

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

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

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

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

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

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

As of June 29, 2018, the aggregate market value of the registrant's voting and non-voting common stock held by non-affiliates was approximately $132.4 million based on a closing price of $9.15 per share as quoted by The Nasdaq Global Select Market as of such date. In determining the market value of non-affiliate common stock, shares of the registrant's common stock beneficially owned by officers, directors and affiliates have been excluded. This determination of affiliate status is not necessarily a conclusive determination for other purposes.

As of March 15, 2019 there were 28,055,344 shares of common stock, $0.0001 par value per share, outstanding.

DOCUMENTS INCORPORATED BY REFERENCE

Part III of this Annual Report on Form 10-K incorporates by reference certain information from the registrant's definitive Proxy Statement for its 2019 annual meeting of shareholders, scheduled to be held on May 8, 2019 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 end of December 31, 2018. Except with respect to information specifically incorporated by reference in this Form 10-K, the Proxy Statement is not deemed to be filed as part of this Form 10-K.

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SPECIAL NOTE REGARDING FORWARD-LOOKING STATEMENTS AND INDUSTRY DATA

This Annual Report on Form 10-K contains forward-looking statements that involve substantial risks and uncertainties. All statements, other than statements of historical facts, contained in this Annual Report on Form 10-K, including statements regarding our strategy, future operations, future financial position, future revenue, projected costs, prospects, plans and objectives of management and expected market growth are forward-looking statements. The words “anticipate,” “believe,” “continue,” “could,” “estimate,” “expect,” “intend,” “may,” “plan,” “potential,” “predict,” “project,” “should,” “target,” “would” and similar expressions are intended to identify forward-looking statements, although not all forward-looking statements contain these identifying words.

These forward-looking statements include, among other things, statements about:

- our plans to develop and commercialize RTB101 alone or in combination with a rapalog, such as everolimus or sirolimus, and other product candidates for the targeted indications and patient populations, including the therapeutic potential and clinical benefits thereof;
- our ongoing and future clinical trials for RTB101 alone or in combination with a rapalog, such as everolimus or sirolimus, whether conducted by us or by any future collaborators, including the timing of initiation of these trials and of the anticipated results;
- the timing of and our ability to obtain and maintain regulatory approvals for our product candidates;
- the rate and degree of market acceptance and clinical utility of any products for which we receive regulatory approval;
- our commercialization, marketing and manufacturing capabilities and strategy;
- our intellectual property position and strategy;
- our ability to identify additional product candidates with significant commercial potential;
- our plans to enter into collaborations for the development and commercialization of product candidates;
- the potential benefits of any future collaboration;
- our estimates regarding expenses, future revenue, capital requirements and needs for additional financing;
- developments relating to our competitors and our industry; and
- the impact of government laws and regulations.

We may not actually achieve the plans, intentions or expectations disclosed in our forward-looking statements, and you should not place undue reliance on our forward-looking statements. Actual results or events could differ materially from the plans, intentions and expectations disclosed in the forward-looking statements we make. We have included important factors in the cautionary statements included in this Annual Report on Form 10-K, particularly in the “Risk Factors” section, that could cause actual results or events to differ materially from the forward-looking statements that we make. Our forward-looking statements do not reflect the potential impact of any future acquisitions, mergers, dispositions, collaborations, joint ventures or investments that we may make or enter into.

You should read this Annual Report on Form 10-K and the documents that we reference herein and have filed or incorporated by reference as exhibits hereto completely and with the understanding that our actual future results may be materially different from what we expect. We do not assume any obligation to update any forward-looking statements, whether as a result of new information, future events or otherwise, except as required by law.

This Annual Report on Form 10-K includes statistical and other industry and market data that we obtained from industry publications and research, surveys and studies conducted by third parties. Industry publications and third-party research, surveys and studies generally indicate that their information has been obtained from sources believed to be reliable, although they do not guarantee the accuracy or completeness of such information. We are responsible for all of the disclosure contained in this Annual Report on Form 10-K, and we believe these industry publications and third-party research, surveys and studies are reliable.

PART I

Unless the context requires otherwise, references in this Annual Report on Form 10-K to the "Company," "resTORbio," "we," "us," and "our" refer to resTORbio, Inc. and its subsidiary. Our "board of directors" refers to the board of directors of resTORbio, Inc. All brand names or trademarks appearing in this report are the property of their respective owners.

Item 1. Business.

Overview

We are a clinical-stage biopharmaceutical company developing innovative medicines that target the biology of aging to prevent or treat age-related diseases with the potential to extend healthy lifespan. Our lead program selectively inhibits the target of rapamycin complex 1, or TORC1, an evolutionarily conserved pathway that contributes to the decline in function of multiple organ systems. Our lead product candidate, RTB101, is an oral, selective, and potent inhibitor of TORC1. RTB101 inhibits the phosphorylation of multiple targets downstream of TORC1. Inhibition of TORC1 has been observed to extend lifespan and healthspan in aging preclinical species and to enhance immune, neurologic and cardiac functions, suggesting potential benefits in several aging-related diseases. We have successfully completed a Phase 2b clinical trial in our initial indication to reduce the incidence of respiratory tract infections, or RTIs, in the elderly regardless of the causative pathogen, and based on communications to date, including an end of Phase 2 meeting with the U.S. Food and Drug Administration, or FDA, we plan to initiate Phase 3 clinical trials in the second quarter of 2019.

The decline in immune function that occurs during aging, or immunosenescence, increases susceptibility to a variety of diseases, including RTIs, that significantly contribute to morbidity and mortality in the elderly. Our initial focus is on the development of RTB101 as a first-in-class immunotherapy designed to improve immune function and thereby reduce respiratory illness in the elderly regardless of the causative pathogen. Our TORC1 immunotherapy approach is supported by two randomized, placebo-controlled Phase 2 clinical trials which enrolled more than 900 elderly subjects and provided statistically significant (defined as nominal $p < 0.05$) and clinically meaningful results. In 2018, we reported results from our exploratory dose-ranging randomized, placebo-controlled Phase 2b clinical trial in 652 elderly patients at increased risk of RTI-associated morbidity and mortality defined as aged 85 and over, or 65-84 with one or more comorbidities including: asthma, chronic obstructive pulmonary disease, or COPD, type 2 diabetes mellitus, or T2DM, or current smoker.

The results from this trial demonstrated a statistically significant and clinically meaningful 30.6% reduction in the percentage of patients with one or more laboratory-confirmed RTIs, the primary endpoint of the trial, in the RTB101 10 mg once daily cohort compared to the placebo cohort. Prespecified analyses of the patient populations enrolled in the trial demonstrated (i) a statistically significant 52.1% reduction in the percentage of patients with severe laboratory-confirmed RTI symptoms in the RTB101 10 mg once daily cohort compared to the placebo cohort, (ii) a statistically significant 66.7%, 68.9%, and 25.3% reduction in the prespecified endpoint of patients 85 and older, 65 and older with asthma and 65 and older with T2DM, respectively, with one or more laboratory-confirmed RTIs in the RTB101 10 mg once daily cohort compared to the placebo cohort, and (iii) no reduction in the incidence of laboratory-confirmed RTIs in patients who were current smokers or with COPD in the RTB101 10 mg once daily cohort compared to the placebo cohort. The lack of efficacy observed in current smokers and patients with COPD is consistent with pre-clinical data suggesting that mTOR inhibition exacerbates cigarette smoke-induced lung inflammation in COPD. The combination of RTB101+everolimus and the RTB101 10 mg twice daily did not meet the primary endpoint, suggesting that less TORC1 inhibition with RTB101 10 mg once daily may be more beneficial for reducing the incidence of RTIs in high risk elderly patients. We believe the collective results from our Phase 2a and Phase 2b clinical trials enrolling more than 900 elderly subjects suggest that RTB101 10 mg once daily, if successfully developed and approved, may improve the function of the aging immune system and reduce the incidence of clinically symptomatic respiratory illness in elderly patients. In our planned Phase 3 program, we expect to enroll elderly subjects 65 and older, excluding current smokers and COPD patients.

We observed additional positive results from prespecified analyses for any infection and urinary tract infections, or UTIs, in our Phase 2b trial, such as (i) a statistically significant 23.6% reduction in the percentage of patients with any infection in the RTB101 10 mg once daily cohort compared to the placebo cohort, (ii) a statistically significant 74.6% reduction in the percentage of patients with one or more UTIs in the RTB101 10 mg twice daily cohort and (iii) a 34.4% reduction in patients with one or more UTIs in the RTB101 10 mg once daily cohort. Recent scientific findings, including those published in the scientific journals *Cell*, *Nature* and *Science*, suggest that aging and aging-related conditions, such as immunosenescence, may be attributable not only to random cellular wear and tear, but also to specific intra-cellular signaling pathways, including the mTOR pathway. mTOR is a protein kinase that signals via two multiprotein complexes, known as

TORC1 and TORC2. TORC1 inhibition has been observed to prolong lifespan, enhance immune function, ameliorate heart failure, enhance memory and mobility, decrease adiposity, and delay the onset of aging-related diseases in multiple animal studies. Specifically, with respect to enhanced immune function, TORC1 inhibition was observed in preclinical studies to rejuvenate blood, or hematopoietic, stem cell function, increase infection-fighting white blood cell production and enhance antibody-mediated, or adaptive, immunity. On the other hand, TORC2 inhibition has been observed to decrease lifespan in preclinical studies and cause unwanted side effects of hyperlipidemia and hyperglycemia in certain animals and humans. Therefore, based on these observations and data from more than 900 patients enrolled in our Phase 2a and Phase 2b clinical trials, we believe our TORC1 program has the potential to improve immune function and counteract immunosenescence in the elderly.

The reduced ability of elderly subjects to effectively detect and fight infections is most commonly manifested in their susceptibility to RTIs and the negative effects such infections have on their overall health. RTIs are the second leading cause of hospitalization in people age 85 and over, and the fourth leading cause in people age 65 and over, contributing to high healthcare costs that are three to five times higher than for the elderly population than for the younger population. Furthermore, antibiotics, which are ineffective against viruses, are often prescribed indiscriminately to treat RTIs, which may cause side effects and contribute to the growing global problem of antibiotic resistance. As the elderly represent the fastest growing population in the world, we believe there is significant unmet medical need for innovative therapeutic options for reducing the incidence of RTIs by improving the function of the aging immune system.

We believe our approach to addressing RTIs in the elderly possesses several clinical and commercial advantages. Our TORC1 program offers an immunotherapy approach that has the potential to address a broad range of viral and bacterial pathogens. Statistically significant and clinically meaningful reductions in RTI incidence were observed in our Phase 2a and Phase 2b clinical trials with RTB101 10mg once daily. We believe the risk-to-benefit ratio of our program observed in clinical studies to date is well-suited to the elderly due to the following observations: our oral product candidates were well-tolerated in elderly subjects, none of the participants in the active treatment arms experienced a serious adverse event that was related to the study drug, and the doses being investigated in our Phase 2b clinical trial were 60 to 240 times lower than maximum tolerated doses established in prior clinical trials for other indications. Based on communications to date with the U.S. Food and Drug Administration, or FDA, including an end of Phase 2 meeting, we plan to initiate a Phase 3 clinical program in the second quarter of 2019. We plan to conduct pivotal clinical trials and to seek regulatory approval for commercialization of RTB101 in the United States and Europe. Separate pivotal trials may be conducted to support potential approvals in Japan and China. In some markets, we may collaborate with third parties for the development and commercialization of our product candidates.

We licensed the worldwide rights to our TORC1 program, including RTB101 alone or in combination with everolimus, from Novartis International Pharmaceutical Ltd., or Novartis, in March 2017. Our management team includes our co-founders, Chen Schor, who serves as our President and Chief Executive Officer, Joan Mannick, M.D., who serves as our Chief Medical Officer, Meredith Manning, who serves as our Chief Commercial Officer, and additional veterans in drug development and discovery, with executive experience in leading global pharmaceutical companies. Dr. Mannick led the TORC1 clinical program at Novartis Institutes for Biomedical Research, Inc., or NIBR, prior to our in-licensing of the program. We are supported by investors that include both private equity venture capital funds and public healthcare investment funds.

Our Strategy

Our goal is to be a leading biopharmaceutical company focused on treating aging-related diseases. We strive to maintain a leadership position in the TORC1 inhibitor class of pharmaceutical products for aging-related diseases. The key elements of our strategy to achieve this goal include:

- *Rapidly advance our TORC1 program as immunotherapy for reducing the incidence of clinically symptomatic respiratory illness in elderly subjects.* In July 2018, we reported positive topline data from our Phase 2b clinical trial of RTB101 alone and in combination with everolimus in elderly subjects at increased risk of mortality and morbidity due to RTIs. In that trial, RTB101 10 mg once daily reduced the incidence of RTI by 30.6% in the populations studied in the trial. Based on the topline results and communications to date including an end of Phase 2 meeting with the FDA, we plan to initiate pivotal clinical trials in the second quarter of 2019 where we will study RTB101 10 mg once daily in subjects 65 years and older, excluding current smokers and COPD patients. The goal of the pivotal trials is to potentially submit an application for regulatory approval of RTB101 in the United States, Europe and additional countries.

- *Develop our TORC1 program for additional indications.* We also intend to develop RTB101, alone or in combination with a rapalog, such as everolimus and sirolimus, for the treatment of additional aging-related diseases based on preclinical and clinical evidence on the effects of TORC1 inhibition. We believe that there is strong rationale to support the investigation of RTB101, alone or in combination with a rapalog, for the

prevention and treatment of additional aging-related indications, including other infections, for example, urinary tract infections, neurodegenerative diseases and heart failure.

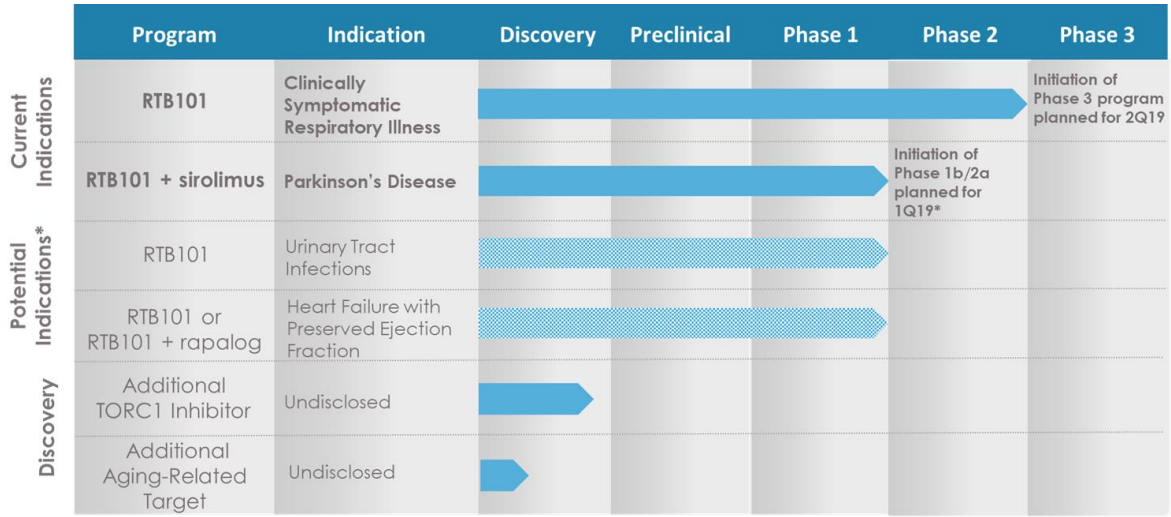
- *Commercialize our product candidates in the United States and potentially collaborate with others globally to maximize their commercial value.* We plan to directly commercialize our product candidates in the United States with a sales force mainly targeting pulmonologists and geriatricians with a high flow of patients 65 years of age and above. We may consider collaborating with third parties to broaden the distribution of our product candidates in the United States. In other markets for which commercialization may be less capital efficient for us, we may selectively pursue strategic collaborations with third parties in order to maximize the commercial potential of our product candidates. We believe there are significant opportunities to market RTB101, if approved, in Europe and Japan, which we may choose to pursue in collaboration with others.

- *Maintain and grow a robust intellectual property portfolio in the field of TORC1 inhibition for aging-related diseases.* We have an exclusive license to ten patent families directed to compositions of matter, methods of use and formulations covering RTB101 alone or in combination with everolimus and have filed additional method of use patent applications. We intend to aggressively pursue and maintain broad intellectual property protection for RTB101 alone or in combination with a rapalog, such as everolimus or sirolimus, or other compounds for the prevention of RTIs and the prevention or treatment of other aging-related diseases through U.S. and international patents.

- *Develop, acquire or in-license product candidates that enhance our global leadership position.* We have additional TORC1 inhibitor compounds in discovery that we may develop, and we may acquire or in-license other product candidates targeting TORC1 and other pathways that regulate aging to support our goal to be the leading biopharmaceutical company focused on the treatment of aging-related diseases.

Our Product Pipeline

The following table summarizes key information about our product candidates.



*For heart failure with preserved ejection fraction, and certain other infections, we may be required to file an investigational new drug application, or IND, prior to initiating Phase 2 clinical trials. We expect to have the ability to initiate these Phase 2 clinical trials without the need to conduct prior Phase 1 clinical trials.

Aging and its Regulation by the mTOR Pathway

Advances in the scientific understanding of aging have until recently been limited, despite high growth in the elderly population

The elderly are the fastest growing population around the globe. According to the U.S. Census Bureau, the population age 65 and older in the United States is expected to double by 2050 compared to 2012 estimates. According to global census data, there are nearly 150 million people age 65 and older, and approximately 20 million people age 85 years

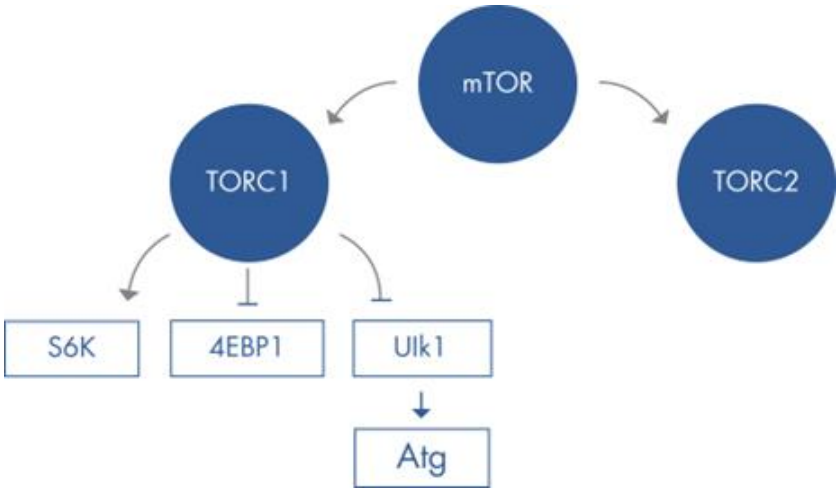
and older in the United States, the major European countries and Japan. Despite age being the major risk factor for multiple chronic diseases, we believe few therapies are being developed to target the aging immune system, and none have been approved.

mTOR is an evolutionarily conserved pathway that regulates aging

mTOR is a serine/threonine protein kinase that regulates the process of aging and aging-related diseases and conditions. Inhibition of the mTOR pathway has been observed to prolong lifespan in multiple animals. These data support the potential for drugs that target the mTOR pathway to have therapeutic benefits for aging and aging-related conditions in humans.

In preclinical studies, the mTOR pathway has been observed to be hyperactivated in some cell types, including hematopoietic stem cells, or HSCs, at an advanced age. It was observed that suppressing mTOR activity in these cell types to levels found at younger ages may enhance cell function, including their ability to generate white blood cells. Furthermore, preclinical studies found that mTOR activity stimulates protein synthesis and cell growth but inhibits protective processes such as autophagy in which damaged proteins and organelles are broken down and recycled. Therefore, these studies suggest that increased mTOR activity is beneficial during years of growth and reproduction but may be harmful during post-reproductive years when cells accumulate damage and require protective mechanisms such as autophagy to prevent and repair damage.

mTOR signals via two multiprotein complexes, known as TORC1 and TORC2. TORC1 inhibition has been observed to prolong lifespan, enhance immune responses, ameliorate neurodegenerative diseases, ameliorate heart failure, enhance memory and mobility, decrease adiposity and delay onset of aging-related diseases in multiple animal studies. On the other hand, TORC2 inhibition has been observed to decrease lifespan and cause hyperlipidemia and hyperglycemia in certain animals and humans. Therefore, we believe the optimal approach for the treatment of aging-related conditions through mTOR inhibition is a regimen that inhibits TORC1 without inhibiting TORC2. mTOR within the TORC1 complex introduces phosphates to, or phosphorylates, multiple proteins including S6K, 4EBP1 and Ulk1, as shown in the figure below. Different dosing regimens that inhibit different spectrum of TORC1, as measured by decreased phosphorylation of multiple proteins downstream of TORC1, may be more beneficial for the prevention or treatment of certain aging-related diseases.



We believe TORC1 inhibition may have therapeutic benefit in multiple aging-related diseases. Preclinical studies suggest that key mechanisms involved in the anti-aging effects of TORC1 inhibition include improved stem cell function, increased autophagy, increased expression of mitochondrial proteins that are important for energy production, decreased adiposity and increased expression of proteins that are responsible for cellular maintenance and repair. Based on preclinical data, these biological effects have the potential to improve multiple aging-related pathologies:

1. *Decreased immune function and increased risk of infections.* The immune system has several important functions, including protection against harmful pathogens, cancer immunosurveillance and clearance of senescent cells. Innate immunity is the body's first line of defense against a wide range of pathogens, while

adaptive immunity is a more pathogen-specific immune response that develops over time. Immune cells are produced by HSCs in the bone marrow, which can lose functionality with age. In preclinical studies, aged dendritic cells, a type of innate immune cell, demonstrated defective Type 1 interferon production, a central component of anti-viral immunity, in response to a virus. This response is consistent with the observation that dendritic cells from older subjects produced less interferon upon stimulation with a virus than those from younger subjects. Adaptive immunity also declines with age. The number and functionality of certain white blood cells known as lymphocytes, including antibody-producing B lymphocytes, have been observed to be decreased in elderly human subjects. We believe that this decline in immune function contributes to the higher incidence of common infections such as respiratory and urinary tract infections in the elderly.

2. *Decreased mitochondrial function and organ dysfunction.* During aging, mitochondrial function, which is important for metabolism and energy production in cells, is diminished. This diminution is linked to a switch from more efficient fatty acid oxidation to less efficient glucose oxidation in aging organs. The detrimental nature of this metabolic change has been extensively described in animal and human studies of aging-related conditions, including heart failure.

3. *Decreased autophagy and accumulation of damaged proteins*. Autophagy is the process in which a cell breaks down and recycles damaged cellular components, including damaged and aggregated proteins. Preclinical data suggests that an aging-associated decrease in autophagy leads to the accumulation of toxic proteins and may result in aging-associated pathologies such as neurodegeneration.

Immunosenescence and Respiratory Tract Infections in the Elderly

Potential for TORC1 inhibition to address decreased immune function associated with aging

TORC1 inhibition has been observed to enhance immune function in at least three independent preclinical studies to date, conducted by laboratories at the University of Michigan, Emory University and St. Jude Children's Research Hospital, where administration of mTOR inhibitors improved immune response to influenza vaccination. Further, findings from these preclinical studies suggest that short-term treatment of aged animals with a TORC1 inhibitor can rejuvenate HSC function, increase the number of infection-fighting white blood cells, and increase longevity. A recent study conducted by laboratories at St. Jude Children's Research Hospital also showed that RTB101 improved survival in mice treated with a lethal dose of influenza virus. We believe these findings, as well as results from our Phase 2 clinical studies, suggest that TORC1 inhibition has the potential to improve immune function and reduce the incidence of clinically symptomatic respiratory illness in elderly humans.

Respiratory tract infections in the elderly

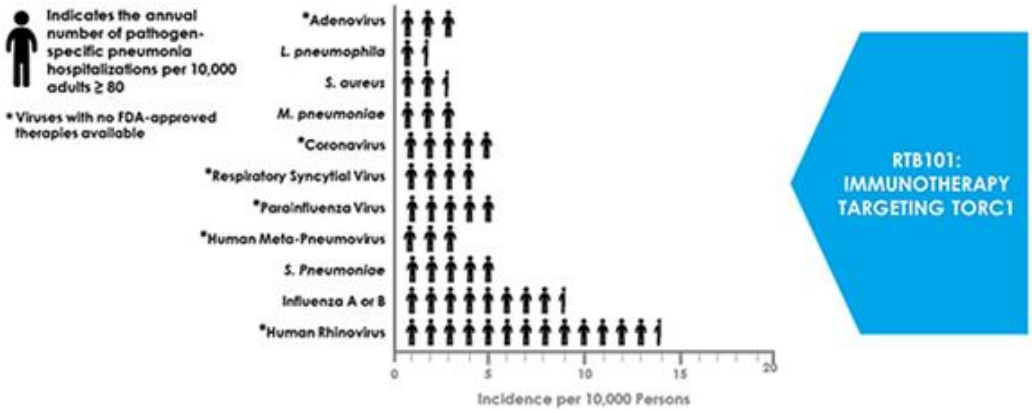
The reduced ability of the aging immune system to effectively detect and fight infections results in increased susceptibility of the elderly to RTIs, which, in turn negatively impacts such patients' overall health and quality of life. We believe that decreasing the incidence of RTIs is a large unmet medical need in the elderly, particularly in subjects at an increased risk of RTI-related morbidity and mortality. We believe there is a significant unmet medical need for an innovative therapy to reduce the incidence of RTIs in the elderly for the following reasons:

- *The large and growing elderly population is particularly susceptible to morbidity and mortality from RTIs.* The elderly represent the fastest growing population across the globe. In the United States, RTIs are the second leading cause of hospitalizations in people age 85 and over and the fourth leading cause of hospitalizations in people age 65 and over. Mortality among people age 75 and over is highest each year during winter cold and flu season. Age is a risk factor for RTIs, with men aged 85-89 experiencing lower RTIs at twice the rate of men aged 65-69. As a result, RTIs, which are typically not serious in healthy adults, are exacerbated in the elderly. Approximately 62% of elderly aged 65 and older have comorbidities. Elderly patients with comorbidities may also be at a higher risk of morbidity and mortality due to RTIs as compared to healthy elderly subjects. Comorbidities among the elderly are common, with approximately 7% having asthma, 20% having T2DM and 13% having congestive heart failure, or CHF. Prior to initiating the Phase 2b clinical trial, a market research study with five payors and 55 physicians in the United States was conducted. The results of the research provided further support that the results observed in the Phase 2a clinical trial are potentially clinically meaningful to physicians and that there is an unmet medical need in the elderly, particularly in the elderly at high risk of mortality from RTIs. Phone interviews with payors also illustrated that, subject to FDA approval, payors may be able to include a product with our efficacy and safety profile

into a preferred tier on their formularies and may request a modest rebate. A more recent physician survey was also conducted in April 2018. We surveyed 100 physicians who treat 25,000 elderly patients monthly, which indicated that a therapeutic that reduced the incidence of RTIs by 25% would be considered to have clinically meaningful efficacy. Physicians in the survey would expect to prescribe a therapeutic that reduces the incidence of RTIs by 25-40% to 30-50% of their patients aged 65 and older with certain comorbidities or to patients 85 and older. Topline results from our Phase 2b trial demonstrated a statistically significant reduction in the percentage of patients 65 years and older who are non-smokers and do not have COPD, with one or more laboratory-confirmed RTIs in the RTB101 10 mg once daily cohort compared to placebo. We expect to evaluate RTB101 in subjects 65 years of age and older that do not have COPD and do not smoke in our pivotal trials.

- *RTIs contribute to high healthcare burden and costs*. RTIs are the second leading cause of hospitalization in people age 85 and over, and the fourth leading cause in people age 65 and over, contributing to high healthcare burdens and costs for the elderly population and the healthcare system that are three to five times higher than for the younger population. At least 11% of CHF exacerbations requiring hospitalization and 80% of asthma exacerbations are associated with RTIs. The risk of a cardiovascular event is three to six fold higher after the onset of an RTI than in the absence of infection. Approximately 7% of people aged 85 years and over go to the emergency room with RTIs each year. In addition, two-thirds of people aged 85 and over who go to the emergency room for infection-related reasons are hospitalized, and once hospitalized, one-third of people aged 85 and over are admitted to a nursing home. These statistics illustrate the large economic impact of RTIs on the healthcare system in the United States.

- *The majority of RTIs are caused by viruses for which no available therapy exists*. The majority of RTIs are caused by viruses, most of which lack approved prophylactics or therapies, leaving physicians with few treatment options. Based on Center for Disease Control, or CDC, guidelines, vaccines are given to prevent influenza and pneumococcal infections. However, even if vaccinated, the elderly are less likely to develop sufficient protective immunity against influenza and pneumococcal infections due to immunosenescence. In addition, vaccines against most of the viral pathogens that cause RTIs are not currently available. The following figure illustrates the specific pathogens detected in patients 80 years or older hospitalized with community-acquired pneumonia.



- *Antibiotics are often prescribed indiscriminately to treat RTIs, leading to potential side effects and contributing to growing antibiotic resistance*. Antibiotics, which are ineffective against viruses, are often prescribed indiscriminately to treat RTIs, which may cause side effects related to antibiotic use and contribute to the growing global problem of antibiotic resistance. As antibiotic use is a primary driver of antibiotic resistance, we believe that reducing the incidence of RTIs in the elderly could also indirectly limit the rise of antibiotic-resistant bacteria. Furthermore, the elderly are at increased risk of antibiotic-related adverse events due to increased organ sensitivity, increased exposure due to changes in pharmacokinetics, and polypharmacy. According to a study conducted by McGill University, antibiotics have been linked to 17% of adverse drug-related events in the elderly who visit emergency departments. Antibiotic use can also lead to lethal superinfections such as *C. difficile* infections.

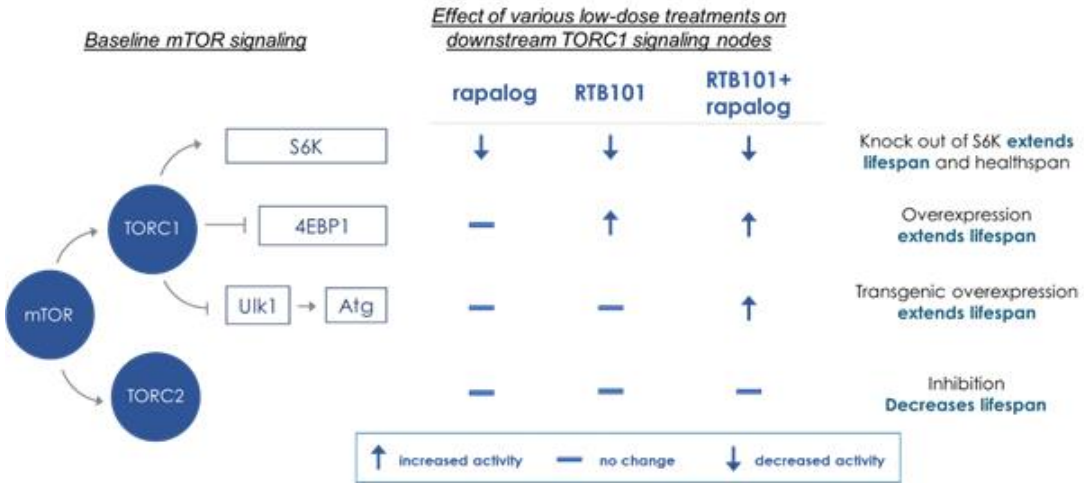
- *Lack of immunotherapy drugs to address RTIs*. Immunotherapies ideally enhance the immune system to provide broad, acute and long-lasting protection against pathogens. Currently, however, there are no approved immunotherapies to enhance immune function in the elderly. We believe RTB101 is a potential immunotherapy aimed at enhancing immune function in the elderly, and thereby decreasing the incidence of clinically symptomatic respiratory illness associated with a broad spectrum of pathogens, particularly viral pathogens. In addition, beyond an individual level, we believe immunotherapies may benefit the wider population through indirect protection that occurs when a large percentage of the population has become immune to a disease, thereby preventing or limiting the spread of infection and providing a measure of protection for individuals who are not immune, a phenomenon known as herd immunity.

Our TORC1 Program

Overview

In March 2017, we obtained a license from Novartis to the worldwide rights to RTB101 for all indications, and the rights to use everolimus in combination with RTB101 for all aging-related indications. RTB101 is an orally administered, small molecule, potent TORC1 inhibitor that binds to the active site of mTOR on the TORC1 complex, a mechanism known as catalytic inhibition. In contrast, rapalogs, such as everolimus or sirolimus, also orally administered small molecules, inhibit mTOR activity by changing the shape of TORC1, a mechanism known as allosteric inhibition, that is distinct from and synergistic with catalytic inhibition.

The downstream signaling cascade of TORC1 that we believe occurs in scenarios of baseline, RTB101 alone and RTB101 in combination with a rapalog, such as everolimus or sirolimus are pictured in the following figure.



Our TORC1 program includes evaluation of RTB101 alone because we believe RTB101 monotherapy can effectively inhibit phosphorylation of multiple downstream signaling nodes of TORC1, specifically S6K and 4EBP1, that are key drivers of TORC1 downstream activity. Decreased phosphorylation of S6K leads to decreased activity, while decreased phosphorylation of 4EBP1 and Ulk1 leads to increased activity. We believe RTB101 alone consistently inhibits more downstream signaling nodes of TORC1 than a rapalog, such as everolimus or sirolimus, alone. Furthermore, we believe RTB101 at the low doses that we are evaluating in our clinical studies can achieve these effects without inhibiting TORC2. RTB101 at higher doses, while able to more completely inhibit TORC1, may also inhibit TORC2, which may lead to undesirable side effects.

Our TORC1 program also includes evaluation of RTB101 in combination with a rapalog, such as everolimus or sirolimus, as the combination of catalytic and allosteric inhibitors may yield complete inhibition of all nodes downstream of TORC1, including 4EBP1 and Ulk1, without affecting TORC2. It was observed in preclinical in vitro studies that RTB101 and everolimus at the comparable doses that we are evaluating in our clinical trials synergistically inhibit S6K and 4EBP1 phosphorylation and induce autophagy. The synergy of RTB101 with everolimus or sirolimus, as measured by Bliss synergy scoring, was up to 150% in those studies. Bliss scores in excess of 30% are considered to be high. Additionally, we believe rapalogs, such as everolimus and sirolimus, may induce a conformation change in TORC1 that allows lower concentrations

of RTB101 to inhibit TORC1 without inhibiting TORC2. Preclinical and clinical data suggest that for some indications, such as reducing the incidence of clinically symptomatic respiratory illness, RTB101 monotherapy may be adequate to yield clinically meaningful benefit to patients, while for other indications, such as neurodegenerative disease and other autophagy-related diseases, the combination of RTB101 and a rapalog, such as everolimus or sirolimus, may be more beneficial. Accordingly, our TORC1 program includes evaluation of both RTB101 alone and in combination with a rapalog, such as everolimus or sirolimus.

Clinical Development of RTB101

Phase 2b Clinical Development

We have completed dosing of all patients in an exploratory, dose-ranging, Phase 2b clinical trial to assess the safety, tolerability and efficacy with RTB101 alone or in combination with everolimus as compared to placebo in elderly patients at increased risk of RTI-related morbidity or mortality. The study enrolled 652 elderly subjects at increased risk of RTI-associated morbidity and mortality, defined as aged 85 and over, or 65-84 with one or more comorbidities or conditions including: asthma, COPD, T2DM, or current smoker. The study was a two-part randomized, double-blind, placebo-controlled clinical trial conducted during winter cold and flu season in the southern hemisphere (Part 1) and northern hemisphere (Part 2). In Part 1, 179 elderly patients were randomized to receive either placebo, RTB101 5 mg or RTB101 10 mg once daily for 16 weeks. At the end of Part 1, an interim analysis was completed by an unblinded data monitoring committee which selected the RTB101 10 mg dose to move forward into Part 2 of the study. In Part 2, 473 elderly patients were randomized to receive either placebo, RTB101 10 mg once daily, RTB101 10 mg twice daily, or RTB101 10 mg in combination with everolimus 0.1 mg once daily. All patients were treated with study drug for 16 weeks, with an additional eight weeks of follow-up off study drug.

The primary endpoint of the study was a reduction, as compared to placebo, in the percentage of patients with one or more laboratory-confirmed RTIs during 16 weeks of treatment. A prespecified exploratory endpoint was the reduction, as compared to placebo, in the percentage of patients with one or more laboratory-confirmed RTIs in each of the following patient subgroups: ≥85 years of age, or 65-84 years of age with asthma, COPD, T2DM, or current smoker. If not otherwise specified, we used a nominal 5% or lower p-value ($p < 0.05$) to define statistical significance for the clinical trials and data presented in this report.

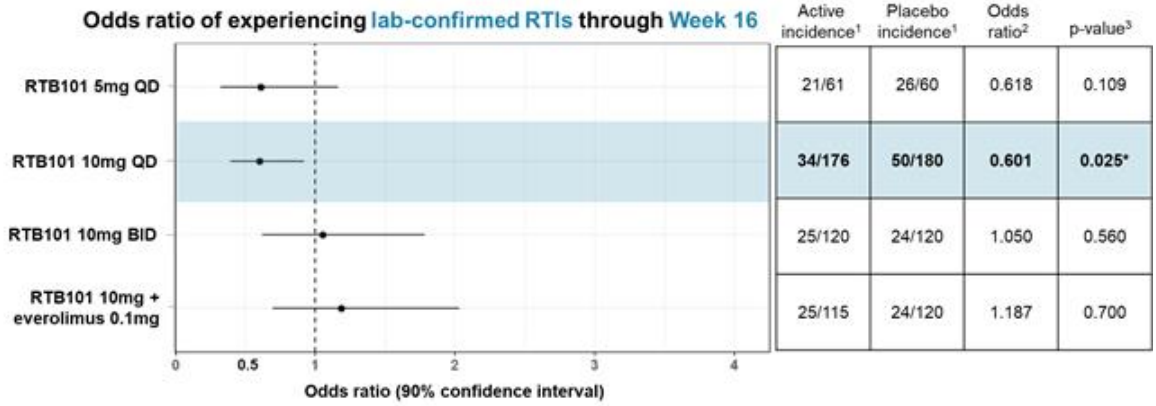
Based on a topline analysis of the primary endpoint, we observed:

- A 30.6% reduction in the percentage of patients who developed one or more laboratory-confirmed RTIs in the RTB101 10 mg once daily cohort as compared to the placebo cohort (odds ratio, or OR, =0.601; p=0.025),

- A 20.6% decrease in the percentage of patients who developed one or more laboratory-confirmed RTIs in the RTB101 5 mg once daily cohort as compared to the placebo cohort (OR=0.618; p=0.109).

- No decrease in percentage of patients who developed one or more laboratory-confirmed RTIs in the RTB101 10 mg twice daily cohort or RTB101 10 mg + everolimus 0.1 mg combination cohort as compared to the placebo cohort.

The odds of experiencing laboratory-confirmed RTIs through Week 16 in all cohorts are also depicted below. The active rate and placebo rate refer to the number of patients in the respective cohorts with laboratory-confirmed RTIs, divided by the number of patients in each cohort.



	Active incidence[1]	Placebo incidence[1]	Odds ratio[2]	p-value[3]
RTB101 5mg QD	21/61	26/60	0.618	0.109
RTB101 10mg QD	**34/176**	**50/180**	**0.601**	**0.025***
RTB101 10mg BID	25/120	24/120	1.050	0.560
RTB101 10mg + everolimus 0.1mg	25/115	24/120	1.187	0.700

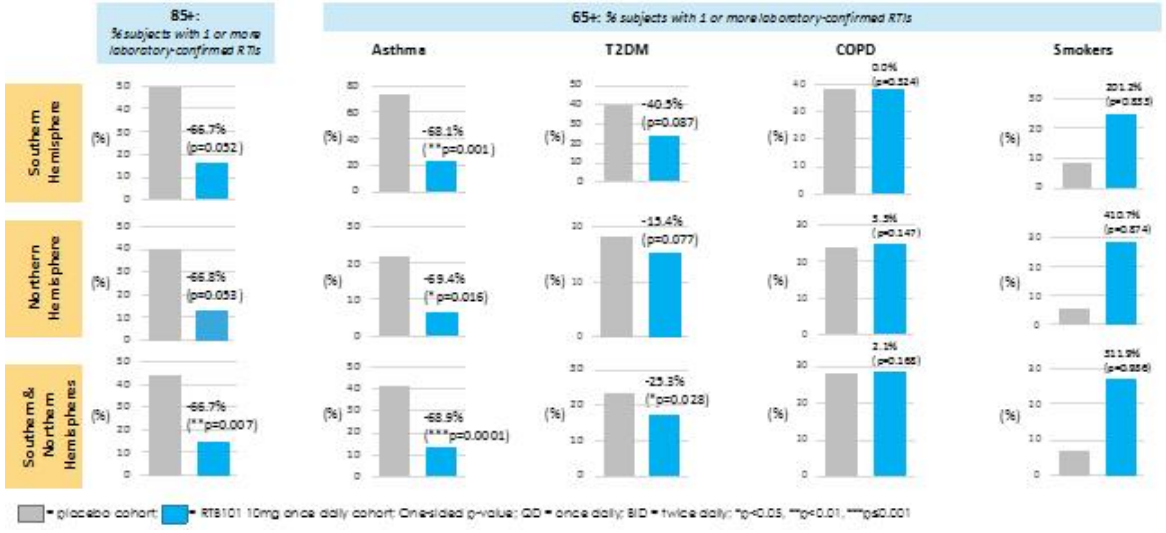
[1]No. of subjects in cohort with one or more laboratory-confirmed RTIs/No. of subjects in cohort; [2]Odds ratio represents the odds of experiencing one or more laboratory-confirmed RTIs in the active treatment group versus the placebo group; [3]One-sided p-value; *p<0.05; QD = once daily; BID = twice daily

To better understand the activity observed in the RTB101 10 mg once daily cohort, a prespecified analysis of each patient subgroup enrolled in the study was conducted. The following decreases in the percentage of patients with laboratory-confirmed RTIs were observed in the RTB101 10 mg once daily cohort as compared to the placebo cohort:

- A 68.9% decrease in all asthma patients (OR=0.105; p=0.0001)
- A 66.7% decrease in all patients 85 years of age and older (OR=0.184; p=0.007)
- A 25.3% decrease in all T2DM patients (OR=0.362; p=0.028)

No decrease in the percentage of patients with laboratory-confirmed RTIs was observed in either COPD patients or current smokers; the lack of efficacy observed in current smokers and patients with COPD is consistent with nonclinical data suggesting that mTOR inhibition exacerbates cigarette smoke-induced lung inflammation in COPD.

The reductions in the percentage of patients with one or more laboratory-confirmed RTIs in the RTB101 10 mg once daily cohort for each patient subgroup in Part 1 and Part 2 are individually depicted in the figure below. The one-sided p-value to compare treatment effect between groups from a logistic regression model, adjusted for prior disease comorbidities and age, is also displayed.



Based on the above analysis of each patient subgroup, we define non-responders as patients with COPD or current smokers. The odds of experiencing laboratory-confirmed RTIs in subjects 65 and older who did not have COPD and are non-smokers are depicted in the figure below.

[1]No. of subjects in cohort with one or more laboratory-confirmed RTIs/No. of subjects in cohort; [2]Odds ratio represents the odds of experiencing one or more laboratory-confirmed RTIs in the active treatment group versus the placebo group; [3]One-sided p-value; **p<0.01; QD = once daily; BID = twice daily

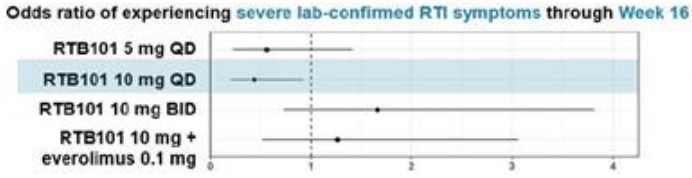
In our planned Phase 3 clinical trials, we expect to evaluate RTB101 10 mg once daily treatment to reduce the percentage of subjects 65 years and older, excluding COPD patients and current smokers, with clinical symptoms consistent with an RTI.

Additional prespecified analyses of secondary and exploratory endpoints were also assessed in our Phase 2b trial:

Severity and incidence of laboratory-confirmed RTIs:

- **Decreased severity of laboratory-confirmed RTI symptoms through 16 weeks of study drug treatment (**Severe RTI symptoms were defined as ones that prevent normal activity):
    - **RTB101 10 mg once daily**: 52.1% reduction in the percentage of patients with severe laboratory-confirmed RTI symptoms compared to placebo (OR=0.437; p=0.034).
    - **RTB101 5 mg once daily**: 41.3% reduction in the percentage of patients with severe laboratory-confirmed RTI symptoms compared to placebo (OR=0.560; p=0.152).
    - No decrease in in the percentage of patients with severe laboratory-confirmed RTI symptoms was observed with RTB101 10 mg twice daily or with RTB101 in combination with everolimus.

The odds of experiencing severe laboratory-confirmed RTI symptoms in all cohorts compared to placebo are individually depicted in the figure below. The active rate and placebo rate refer to the number of patients in the respective cohorts with severe laboratory-confirmed RTI symptoms, divided by the number of patients in each cohort.



Active rate	Placebo rate	Odds ratio	p-value
6/61	10/60	0.560	0.152
8/176	17/180	0.437	0.034*
11/120	7/120	1.661	0.843
8/115	7/120	1.258	0.665

QD=once daily; BID=twice daily; *p<0.05

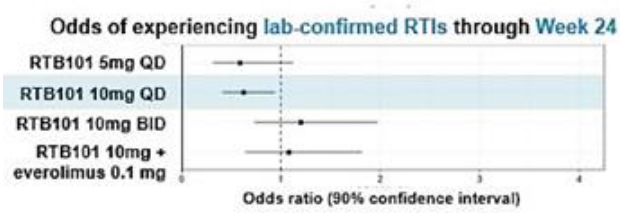
- **Decreased incidence of laboratory-confirmed RTIs over entire 24-week study** (16 weeks of study drug treatment and an additional eight weeks of follow-up)

    - **RTB101 10 mg once daily:** 27.5% reduction in the percentage of patients with laboratory-confirmed RTIs compared to placebo during the 24 weeks (OR=0.623; p=0.030).

    - **RTB101 5 mg once daily:** 19.2% reduction in the percentage of patients with laboratory-confirmed RTIs compared to placebo during the 24 weeks (OR=604; p=0.097).

    - No decrease in percentage of patients with laboratory-confirmed RTIs was observed with RTB101 10 mg twice daily or in combination with everolimus.

The odds of experiencing laboratory-confirmed RTIs over the entire 24-week study in all cohorts compared to placebo are individually depicted in the figure below. The active rate and placebo rate refer to the number of patients in the respective cohorts with laboratory-confirmed RTIs, divided by the number of patients in each cohort.



Active rate	Placebo rate	Odds ratio	p-value
23/61	28/60	0.604	0.097
39/176	55/180	0.623	0.030*
31/120	27/120	1.199	0.725
26/115	27/120	1.079	0.595

QD=once daily; BID=twice daily; *p<0.05

Incidence of total infections of any kind (laboratory-confirmed RTIs and all other infections) during 16 weeks of study drug treatment:

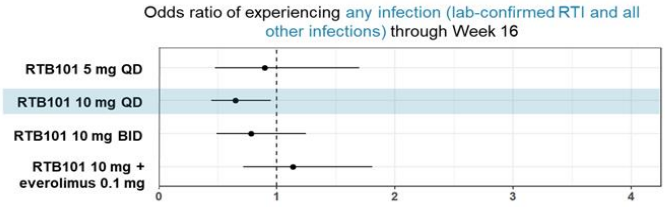
- **Decreased incidence of any infections:**

    - **RTB101 10 mg once daily***:* 23.6% reduction in the percentage of patients with any infection compared to placebo (p=0.032).

    - **RTB101 10 mg twice daily:** 15.4% reduction in the percentage of patients with any infection compared to placebo (p=0.192).

    - No reduction in the percentage of patients with any infection was observed with RTB101 5 mg once daily or with RTB101 in combination with everolimus.

The odds of experiencing an infection in all cohorts compared to placebo are individually depicted in the figure below. The active rate and placebo rate refer to the number of patients in the respective cohorts with any infection, divided by the number of patients in each cohort.



Active rate[1]	Placebo rate[1]	Odds ratio[2]	p-value[3]
33/61	32/60	0.922	0.416
53/176	71/180	0.653	0.032*
33/120	39/120	0.780	0.192
40/115	39/120	1.138	0.676

QD=once daily; BID=twice daily; *p<0.05

Incidence of UTIs during 16 weeks of study drug treatment:

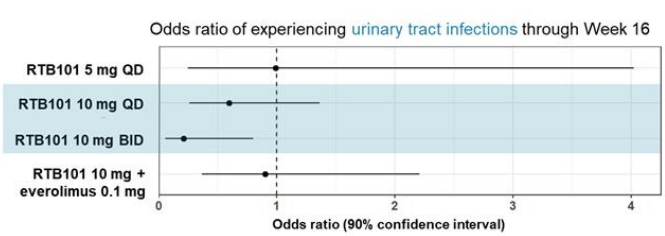
- **Decreased incidence of UTIs:**

- **RTB101 10 mg once daily:** 37.3% reduction in the percentage of patients with one or more UTIs compared to placebo (OR=0.601; p=0.156).

- **RTB101 10 mg twice daily:** 74.6% reduction in the percentage of patients with one or more UTIs compared to placebo (OR=0.211; p=0.027).

- No reduction in the percentage of patients with UTIs was observed with RTB101 5 mg or with RTB101 in combination with everolimus.

The odds of experiencing UTIs in all cohorts compared to placebo are individually depicted in the figure below. The active rate and placebo rate refer to the number of patients in the respective cohorts with UTIs, divided by the number of patients in each cohort.



	Active rate[1]	Placebo rate[1]	Odds ratio[2]	p-value[3]
RTB101 5 mg QD	3/61	3/60	0.994	0.497
RTB101 10 mg QD	7/176	11/180	0.601	0.156
RTB101 10 mg BID	2/120	8/120	0.211	0.027*
RTB101 10 mg + everolimus 0.1 mg	8/115	8/120	0.901	0.424

QD=once daily; BID=twice daily; *p<0.05

In the Phase 2b clinical trial, RTB101 treatment was observed to be well-tolerated. Adverse events, or AEs, were balanced between the RTB101 10 mg once daily and placebo treatment groups. One subject randomized to receive RTB101 10 mg once daily cohort died from traumatic injuries sustained from being hit by a car while riding a bicycle during the 16-week treatment period of the trial, and two subjects (one randomized to receive RTB101 10 mg twice daily and one randomized to receive placebo) died from unknown cause(s) after the week 24 follow-up visit of the trial.. None of the deaths that occurred was attributed to study drug treatment. 4.5% of subjects in the RTB101 10 mg once daily cohort and 7.8% of subjects in the placebo cohort had a serious adverse event, none of which were considered related to study drug. 5.1% of subjects in the RTB101 10 mg once daily cohort and 5.6% of subjects in the placebo cohort discontinued study drug due to an AE. All AEs were mild or moderate except for 12 severe AEs in RTB101 10 mg once daily cohort and 24 severe AEs in the placebo cohort.

Phase 2a Clinical Development

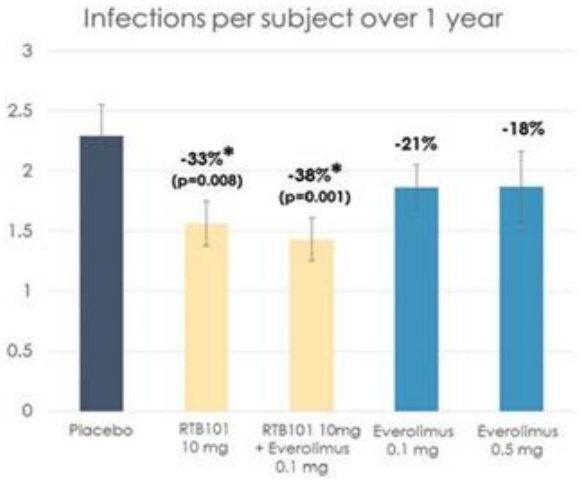
Data from a Phase 2a clinical trial conducted by our licensor, Novartis, were published in July 2018 in Science Translational Medicine, and provide additional support for the efficacy and safety of our clinical program.

The primary objectives of the Phase 2a clinical trial were to assess the safety, tolerability and efficacy of RTB101 alone or in combination with everolimus compared to placebo in enhancing the immune response to vaccination in elderly subjects, as determined by the subjects' immune response to the seasonal influenza vaccine. A prespecified exploratory endpoint assessed the effect of a six-week course of RTB101 alone or in combination with everolimus on infection rates during the year following initiation of study drug treatment. The trial was a double-blinded, placebo-controlled, randomized clinical trial that enrolled a total of 264 male and female subjects at least 65 years of age without underlying unstable medical conditions, and was conducted across 12 trial centers in the southern hemisphere. Subjects were randomized to one of five treatment arms, in which they were administered daily oral doses of everolimus 0.1 mg, everolimus 0.5 mg, RTB101 10 mg, RTB101 10 mg + everolimus 0.1 mg, or placebo. The trial met its primary endpoint of enhancing influenza vaccination response, defined as a greater than 20% increase in antibody concentrations, or titers, to at least two of the three tested influenza vaccine strains as compared to placebo, measured at 12 weeks following initial dosing of the study drug, as well as the prespecified exploratory infection rate endpoint.

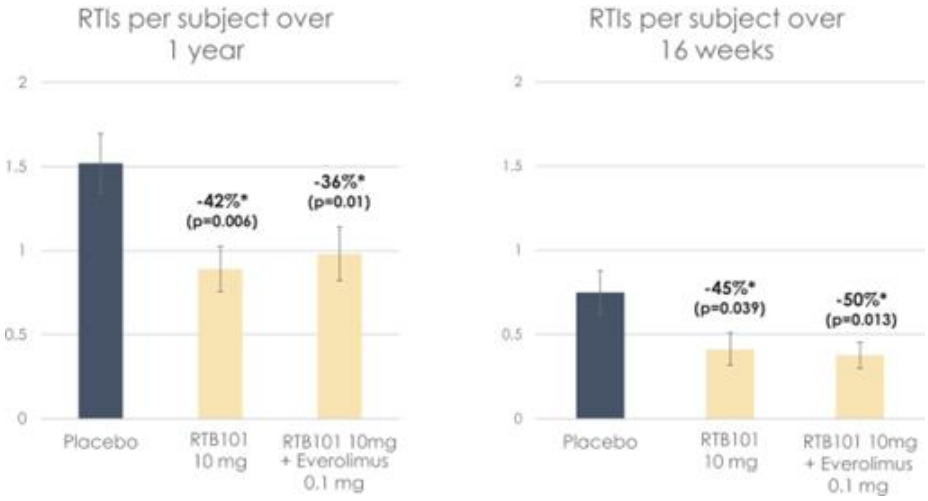
Subjects were treated for six weeks with the study drug and, after a two-week drug-free interval, were given the seasonal influenza vaccine. The subjects were followed for one year following initiation of study drug treatment. The overall infection rate in each treatment group was assessed by having subjects record any infections they experienced during the year following the initiation of study drug treatment in a diary. The sites reviewed the infection diary at each study visit. In addition, sites administered infection questionnaires during phone calls with subjects that occurred weekly during the six-week study drug dosing period and then monthly for the remainder of the trial. Investigators reviewed and approved the

information contained in the telephone questionnaire reports within 24 hours. The infection data in the diaries and telephone reports were reconciled by sites prior to entering infections in the clinical trial database.

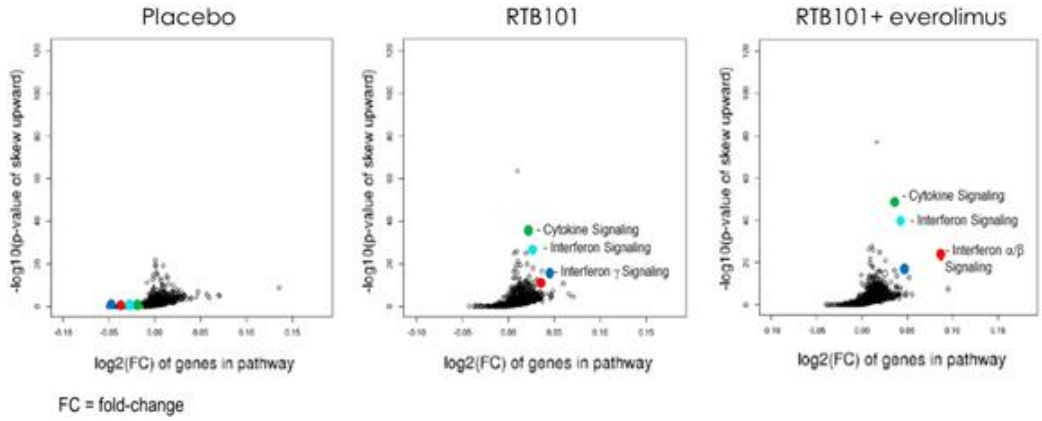
In the RTB101 monotherapy and RTB101 + everolimus combination treatment arms in the intent-to-treat population, statistically significant and clinically meaningful reductions in the annual rate of infections of 33% (p=0.008) and 38% (p=0.001), respectively, compared to placebo, were observed. A lesser, non-statistically significant effect was observed with everolimus monotherapy.



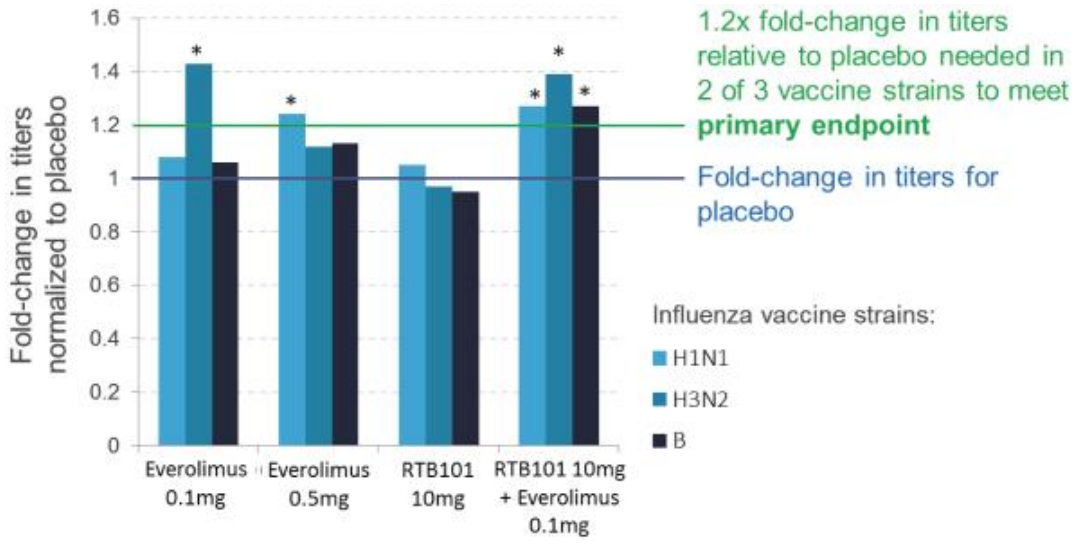
Since the most common infections that occurred during the trial were RTIs, a post-hoc analysis was performed to determine whether a reduction in RTIs contributed to the significant reduction in infections at one year following initiation of study drug treatment in the RTB101 monotherapy and RTB101 + everolimus combination treatment arms. As shown in the figure below, both RTB101 monotherapy and the RTB101 + everolimus combination therapy were observed to reduce the incidence of RTIs at one year by 42% (p=0.006) and 36% (p=0.01), respectively, in the intent-to-treat population. Greater reductions in the incidence of RTIs were observed during the six-week dosing period in the RTB101 monotherapy and RTB101 + everolimus combination arms. Given that the magnitude of the reduction in RTI incidence was greater at six weeks than at one year, these findings suggest that the reduction in RTI rates was greatest during the period when subjects were receiving the study drug. The typical duration of the peak cold and flu season is approximately 16 weeks. As shown in the figure below, analysis of the Phase 2a clinical data also revealed reductions of 45% (p=0.039) and 50% (p=0.013) in RTIs from treatment with RTB101 alone and in combination with everolimus, respectively, during the 16 weeks following initiation of therapy despite only six weeks of treatment.



To assess possible molecular mechanisms underlying the decrease in infection rates in the RTB101 monotherapy and RTB101 + everolimus combination treatment arms, mRNA sequencing analysis of whole blood from subjects at baseline and after six weeks of study drug treatment was conducted. Analysis of whole-blood gene expression data revealed a highly statistically significant up-regulation of pathways related to interferon signaling in the RTB101 monotherapy and RTB101 + everolimus combination treatment arms but not in the placebo arm, as shown in the figures below. These findings suggest that RTB101 alone and in combination with everolimus may improve innate immunity. Genes that were up-regulated the most, including MX1, OAS3, ISG15 and IFIT1, encode a subset of Type 1 interferon-induced proteins that play a critical role in the acute, innate immune response to viruses. Pathways, or groups of genes, related to cytokine signaling and interferon signaling were significantly upregulated, with p-values ranging between 10^{-45} to 10^{-10}.



While the effects of RTB101 monotherapy and RTB101 + everolimus combination therapy on reducing the incidence of RTIs in the elderly and up-regulating innate immunity genes were comparable, only the combination therapy met the primary endpoint of the Phase 2a clinical trial of enhancing influenza vaccination response, defined as a greater than 20% increase in antibody concentrations, or titers, to at least two of the three tested influenza vaccine strains as compared to placebo, measured at 12 weeks following initial dosing of the study drug. We believe these results suggest that the RTB101 + everolimus combination therapy may also enhance the adaptive immune system, given that the RTB101 + everolimus combination resulted in broader TORC1 inhibition.



We believe that the Phase 2a clinical trial results provide proof of concept for the potential therapeutic benefit of RTB101 as immunotherapy to reduce the incidence of RTIs in elderly patients, given the statistically significant and clinically meaningful reduction in RTI rates and the increased expression of innate anti-viral genes observed in RTB101 treatment groups. These Phase 2a results led to the selection of doses for our Phase 2b clinical trials where we confirmed the potential clinical benefits of RTB101 10 mg once daily for reducing the incidence of RTIs in the elderly at increased risk of RTI-associated morbidity and mortality.

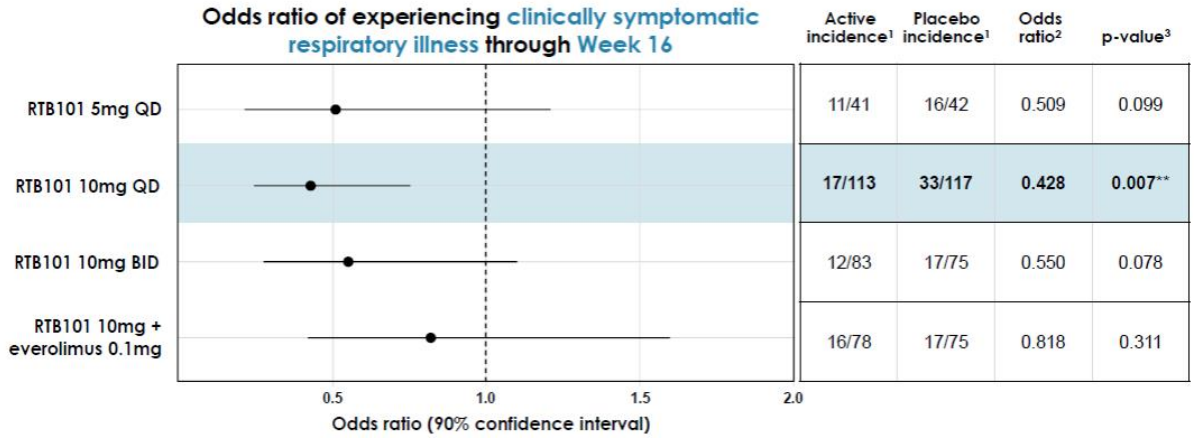
Phase 3 Clinical Development Plan

During the first quarter of 2019, we conducted an end of Phase 2 meeting with the FDA. Alignment was reached with the FDA on key elements of the Phase 3 clinical trials that will support the submission of a New Drug Application, or NDA, for RTB101. Based on our communications with the FDA to date, we plan to conduct two randomized, double-blinded, placebo-controlled Phase 3 clinical trials during the winter cold and flu season to assess the safety and efficacy of 16 weeks of treatment with RTB101 10 mg once daily for the reduction, as compared to placebo, in the percentage of subjects with clinical symptoms consistent with an RTI. We expect to enroll elderly subjects, age 65 and older, excluding current smokers and COPD subjects, randomized 1:1 RTB101 to placebo. We expect the primary endpoint of the Phase 3 clinical trials to be a reduction, as compared to placebo, in the percentage of subjects with clinical symptoms consistent with a respiratory tract infection based on prespecified diagnostic criteria (defined as clinically symptomatic respiratory illness) with or without confirmation of a laboratory pathogen. We also expect a secondary endpoint to be the reduction in the percentage of subjects with clinically symptomatic respiratory illness associated with a laboratory-confirmed pathogen. Consistent with the Phase 2b endpoints, the Phase 3 endpoints include prespecified diagnostic criteria that encompass multiple types of RTIs.

Each of the planned Phase 3 clinical trials is expected to be powered at greater than or equal to 90% to demonstrate a 30% reduction in the percentage of subjects with clinically symptomatic respiratory illness. The first Phase 3 clinical trial is planned to begin in the southern hemisphere in the second quarter of 2019 and is expected to enroll approximately 1,000 subjects. The second Phase 3 clinical trial is planned to begin in the northern hemisphere in the fourth quarter of 2019 and is expected to enroll approximately 1,600 subjects. The number of subjects randomized to receive RTB101 10 mg once daily in the Phase 2b and planned Phase 3 program is expected to reach at least 1,500 which, based on our communications with the FDA, is the safety database that we believe will be sufficient to support an NDA filing, barring any safety signals observed in the Phase 3 trials. Depending on enrollment in the planned Phase 3 clinical trials, we expect topline data from the Phase 3 clinical trials in 2020.

In an analysis of our Phase 2b clinical trial results, a 46.6% reduction in the percentage of subjects with clinically symptomatic respiratory illness was observed in subjects age 65 and older who did not have COPD or smoke, the proposed Phase 3 patient population, when treated with RTB101 10mg once daily as compared to placebo (p=0.007).

The odds of experiencing clinically symptomatic respiratory illness in all cohorts compared to placebo are depicted in the figure below. The active incidence and placebo incidence refer to the number of subjects in the respective cohorts with clinically symptomatic respiratory illness, divided by the number of subjects in each cohort.



[1]No. of subjects in cohort with one or more clinically symptomatic respiratory illness/No. of subjects in cohort; [2]Odds ratio represents the odds of experiencing one or more clinically symptomatic respiratory illness in the active treatment group versus the placebo group; [3]One-sided p-value; **p<0.01; QD = once daily; BID = twice daily

Safety Data from Clinical and Preclinical Development at High Doses of RTB101 Alone and in Combination with Everolimus

Originally, RTB101 was developed for oncology indications. In preclinical studies, at doses higher than those we are currently developing, RTB101 was found to prevent cellular proliferation and tumor progression. Clinical trials in humans were conducted under two open INDs for RTB101 filed with the FDA Division of Oncology Products. More than 440 oncology patients have been treated with RTB101 alone in doses up to 1,600 mg per day, or in combination with other drugs including 200 mg of RTB101 in combination with 2.5 mg of everolimus per day. RTB101 has also been administered to more than 60 healthy volunteers in pharmacokinetic, or PK, studies at doses of up to 1,000 mg per day. To date, the majority of the reported AEs were mild or moderate and include gastrointestinal disturbances, fatigue, decreased appetite, rash and thrombocytopenia, which are consistent with those that have been reported for marketed mTOR inhibitors such as sirolimus and everolimus. No dose-limiting toxicities occurred at doses less than 800 mg per day, and the maximum tolerated dose for RTB101 as a monotherapy was established at 1,200 mg per day. For the prevention of clinically symptomatic respiratory illness, we are developing RTB101 at a daily dose of 10 mg, 120 times lower than the established maximum tolerated dose, and therefore expect the RTB101 to have an acceptable tolerability profile for decreasing the incidence of clinically symptomatic respiratory illness.

Standard preclinical safety and good laboratory practice, or GLP, toxicology studies, up to six months in rats and dogs, have been completed for RTB101, which we believe support the clinical development of the program.

Other Potential Indications for Our TORC1 Program

We may evaluate RTB101 alone or in combination with a rapalog, such as everolimus or sirolimus, or other drugs for the treatment of additional indications, such as Parkinson's disease, urinary tract infections, heart failure with preserved ejection fraction, Huntington's disease and amyotrophic lateral sclerosis. We plan to initiate a Phase 1b/2a clinical trial in the first quarter of 2019 for Parkinson's disease. We expect to select indications based on strong scientific rationale, preclinical or clinical data, unmet medical need and other relevant considerations.

Parkinson's disease

Parkinson's disease, or PD, is a progressive neurodegenerative disease that affects approximately 7.5 million people worldwide. The incidence of PD increases rapidly in people 60 years of age and older, with a mean age at diagnosis of 70.5 years. Glucocerebrosidase, or GBA1, gene mutations are the most common of the currently known PD genetic mutations and up to 10 percent of people with PD in the United States carry it. Patients with PD develop shaking, rigidity, slowness of movement and difficulty walking. Similar to Huntington's disease, PD may be attributed in part to neuronal damage caused by the accumulation within neurons of abnormal aggregates containing the protein α-synuclein. Preclinical studies in mouse models of PD have shown that mTOR inhibition can induce autophagy, reduce α-synuclein accumulation and decrease neuronal cell death. Therefore, induction of autophagy with RTB101 in combination with a rapalog may have therapeutic benefit for patients with PD.

Prevention of recurrent urinary tract infections

Urinary tract infections, or UTIs, are the most common bacterial infection in the elderly, especially in women. Recurrent UTIs are typically defined as 3 or more UTIs within 12 months, or two or more occurrences within six months. Nearly 10% of women age 65 and older and nearly 30% of women age 85 and over report having a UTI annually, and more than half of women older than 55 have been observed to have a UTI recurrence within one year in a primary care setting. Healthcare resource utilization costs due to UTIs are significant, with elderly women having the highest growth in incidence of hospitalizations for UTIs (23.1% per year for women age 80-89). In 2011, UTI-related hospitalizations in the U.S. resulted in a total of $2.8 billion in healthcare costs. UTIs are also the most common reason for antibiotic prescriptions in older adults. Currently, continuous daily low-dose antibiotic prophylactic regimens are used to prevent recurrence of symptomatic UTIs and contribute to the development of multidrug resistant bacteria.

Treatment of viral respiratory tract infections

In the Phase 2a clinical trial, an increase in the expression of innate antiviral gene pathways was observed in the RTB101 10 mg monotherapy and RTB101 10 mg + everolimus 0.1 mg combination arms. We may conduct a biomarker study to assess the speed at which antiviral genes are upregulated after elderly subjects are treated with RTB101. If we observe a rapid increase of antiviral gene expression, we believe RTB101 may have therapeutic benefit for the treatment of viral RTIs.

Heart failure with preserved ejection fraction

Heart failure is one of the most common causes of hospitalizations in people age 65 and older. Heart failure with preserved ejection fraction, or HFpEF, affects about 2.25 million people in the United States, and almost 4 million in Europe and Japan. HFpEF predominantly affects elderly subjects, particularly older women, in whom 90% of new heart failure cases are HFpEF. Patients with HFpEF experience the clinical symptoms of heart failure, despite having the percentage of total blood in the left ventricle of the heart that is pushed out with each heartbeat, known as ejection fractions, in the normal range. These symptoms are attributable in part to stiffened heart muscle that limits blood flow into the heart, known as diastolic dysfunction. Outcomes following hospitalization for decompensated HFpEF are poor. Approximately one third of patients are rehospitalized or die within 90 days of discharge. To date, there are no FDA approved therapies to reduce hospitalization or mortality for HFpEF.

According to scientific literature published by research groups at the Harvard Stem Cell Institute and the University of Washington, aging mice develop stiffened heart muscle and diastolic dysfunction similar to elderly humans with HFpEF. Preclinical studies have shown that a 10-week course of mTOR inhibitor therapy reverses diastolic dysfunction in aging mice. This beneficial effect is likely partly due to an increase in proteins involved in mitochondrial function and fatty acid oxidation. Fatty acids are the predominant substrate used in mitochondrial energy production in healthy adults, but are replaced by glucose as the preferred substrate in heart failure. The shift to glucose as a substrate results in less ATP production by mitochondria. Since ATP is the main cellular fuel, a decrease in ATP production may contribute to heart failure. mTOR inhibitors shift mitochondria back to using fatty acids as a substrate and as a result may increase ATP production in the heart and improve heart function. These findings suggest that RTB101 alone or in combination with a rapalog, such as everolimus or sirolimus, may have potential therapeutic benefit for the treatment of HFpEF in humans.

Huntington's disease

Huntington's disease, or HD, is a disease that affects neurons in the brain and causes movement, psychiatric and cognitive impairment. HD is caused by mutations in a gene encoding protein called huntingtin. Mutant huntingtin forms aggregate in neurons and cause the neurons to degenerate. The mutant huntingtin aggregates can be cleared from neurons by a process called autophagy in which cells remove and recycle intracellular debris including protein aggregates. Preclinical data from brain slices in a HD mouse model has shown that RTB101 in combination with a rapalog, such as everolimus or sirolimus, synergize to prevent neurodegeneration, likely by inducing autophagy and clearing mutant huntingtin aggregates. We believe these findings support the potential that RTB101 in combination with a rapalog, such as everolimus or sirolimus, could have therapeutic benefit for the treatment of HD.

Amyotrophic Lateral Sclerosis

Amyotrophic lateral sclerosis, or ALS, is a fatal, age-related neurodegenerative disorder characterized by progressive loss of both upper and lower motor neurons in the brain and spinal cord. ALS is the most common motor neuron disorder and is estimated to affect 12,000-30,000 people in the United States. The median age of onset of ALS is 64 years, and is characterized by diseased muscle atrophy, spasticity and quadriplegia, culminating in death within three to five years of disease onset due to respiratory failure. Genetic studies of ALS patients have identified mutations in autophagy pathway genes including *p62*/*SQSTM1*, *OPTN*, *TBK1*, *VCP*, and *C9ORF72*. Further, enhancing autophagy has shown benefit in multiple preclinical models of ALS, hence we believe that induction of autophagy with RTB101 in combination with a rapalog, such as everolimus or sirolimus, may have potential therapeutic benefit for patients with ALS.

Intellectual Property

We strive to protect the proprietary technologies that we believe are important to our business, including seeking and maintaining patent protection intended to cover the composition of matter of our product candidates, including RTB101, their methods of use, related technology, and other inventions that are important to our business. We licensed a patent portfolio of ten patent families from Novartis. See "—License Agreement with Novartis." As of March 15, 2019, one family within this patent portfolio covering compositions of matter has 46 issuances in 34 jurisdictions; and has nine pending applications in seven jurisdictions. Our issued patents and pending applications with respect to RTB101 are expected to expire in 2031 or 2032, (depending on eligibility for patent term extension or supplementary protection). Additional pending applications are expected to expire between 2034 and 2037, exclusive of possible patent term adjustments or extensions.

In addition to patent protection, we rely on trade secrets and confidentiality agreements to protect our technology, know-how and other aspects of our business that are not amenable to, or that we do not consider appropriate for, patent protection.

Our success will depend significantly on our ability to obtain and maintain patent and other proprietary protection for commercially important technology, inventions, and know-how related to our business, defend and enforce the patents we own or control, maintain our licenses to use intellectual property owned by third parties, preserve the confidentiality of our trade secrets, and operate without infringing the valid and enforceable patents and other proprietary rights of third parties.

The patent positions of biopharmaceutical companies like us are generally uncertain and involve complex legal, scientific and factual questions. In addition, the coverage claimed in a patent application can be significantly reduced before the patent is issued, and its scope can be reinterpreted after issuance. Consequently, we do not know whether any of our product candidates will be protectable or remain protected by enforceable patents. We cannot predict whether the patent applications we are currently pursuing will issue as patents in any particular jurisdiction or whether the claims of any issued patents will provide sufficient proprietary protection from competitors. Any patents that we hold or control may be challenged, circumvented or invalidated by third parties.

License Agreement with Novartis

In March 2017, we entered into a license agreement with Novartis, pursuant to which we were granted an exclusive, field-restricted, worldwide license to certain intellectual property rights owned or controlled by Novartis, including patents, patent applications, proprietary information, know-how and other intellectual property, to develop, commercialize and sell one or more therapeutic products comprising RTB101 alone or RTB101 and everolimus in a fixed dose combination. Under the license agreement, we have been licensed a patent portfolio of ten patent families directed to composition of matter of RTB101 and its salts, formulations of everolimus and methods of using RTB101 and everolimus to enhance the immune response among others. These families include certain granted patents and pending patent applications in the United States and foreign jurisdictions, including Canada, the United Kingdom, Germany, France, Italy, Spain, Russia, Japan, Korea and China. Patents in these families will begin expiring in 2026, subject to possible patent term extensions. We believe that patent term extension and the potential grant of certain pending patent applications may provide exclusivity for RTB101 and RTB101 + everolimus combination until 2037 in the United States and the major European markets.

The exclusive field for RTB101 is for the treatment, prevention and diagnosis of diseases and other conditions in all indications in humans and animals. With respect to the fixed dose combination of RTB101 and everolimus, the exclusive field of use is for any indication in humans related to the improvement in immune function or immunosenescence in the elderly, the reduction of infection frequency, severity, duration, health care resource utilization, hospitalization, morbidity or mortality, or the treatment of infections, the reduction of pulmonary disease exacerbation frequency, severity, or related hospitalization, the enhancement of therapeutic or prophylactic benefits of vaccines, or any aging-related disease, excluding in each case the application of everolimus in connection with organ transplantation, oncology, immune-oncology or in the cardiac stent field. Novartis has agreed not to enforce any rights to improvements related to RTB101 developed after the effective date in connection with the exercise of our rights under this agreement. In addition, we have agreed to grant back to Novartis for use outside of the exclusive fields any improvements related to everolimus that we develop after the effective date.

We are required to use commercially reasonable efforts to develop and commercialize at least one product in the field in at least one major market, which includes the United States, Japan and certain identified countries in Europe.

As initial consideration for the license, we issued NIBR 2,587,992 shares of our Series A preferred stock.

As additional consideration for the license, we are required to pay up to an aggregate of $4.3 million upon the satisfaction of clinical milestones, up to an aggregate of $24 million upon the satisfaction of regulatory milestones for the first indication approved, and up to an aggregate of $18 million upon the satisfaction of regulatory milestones for the second indication approved. In addition, we are required to pay up to an aggregate of $125 million upon the satisfaction of commercial milestones, based on the amount of annual net sales. We are also required to pay tiered royalties ranging from a mid-single digit percentage to a low-teen digit percentage on annual net sales of products. These royalty obligations last on a product-by-product and country-by-country basis until the latest of (i) the expiration of the last valid claim of a Novartis patent covering a subject product, (ii) the expiration of any regulatory exclusivity for the subject product in a country, or (iii) the 10th anniversary of the first commercial sale of the product in the country, and are subject to a reduction after the expiration of the last valid claim of a Novartis patent or the introduction of a generic equivalent of a product in a country. In addition, if we sublicense the rights under the license agreement, we are required to pay a certain percentage of the sublicense revenue to Novartis. Following the last visit of the 400th subject in our Phase 2b clinical trial, Novartis is no longer entitled to sublicense revenue.

Either we or Novartis may terminate the license agreement if the other party commits a material breach and fails to cure such breach within 60 days after written notice. Novartis may terminate the license agreement upon our bankruptcy,

insolvency, dissolution or winding up. In addition, Novartis may partially terminate the license agreement with respect to everolimus if we fail or cease to use commercially reasonable efforts to research, develop and commercialize a product utilizing everolimus for a period of three years, provided that our license related to RTB101 and Novartis's license to our improvements related to everolimus will continue. In addition, we may terminate the license agreement, with or without cause, in its entirety or on a product-by-product or country-by-country basis, upon 60 days' prior written notice.

Sales and Marketing

We hold worldwide commercialization rights to our product candidates. We do not have our own marketing, sales or distribution capabilities. In order to commercialize our product candidate if approved for commercial sale, we must either develop a sales and marketing infrastructure or collaborate with third parties that have sales and marketing experience. We plan to directly commercialize our product candidates in the United States with a focused sales force targeting top-prescribing physicians with high flow of elderly patients. For some indications, we may also directly commercialize our product candidates in the European Union. In other markets or for certain indications outside the United States for which commercialization may be less capital efficient for us, we may selectively pursue strategic collaborations with third parties in order to maximize the commercial potential of our product candidates.

Manufacturing

RTB101 and rapalogs, such as everolimus or sirolimus, are small molecules that can be manufactured using commercially available technologies. We acquired data from Novartis related to the chemical synthesis and manufacturing of RTB101, which is currently being manufactured by a single contract manufacturing organization, and are outsourcing the manufacturing of rapalogs, such as everolimus or sirolimus.

We believe there are multiple sources for all of the materials required for the manufacture of our product candidates. Our manufacturing strategy enables us to more efficiently direct financial resources to the research, development, and commercialization of product candidates rather than diverting resources to internally develop manufacturing facilities. As our product candidates advance through development, we expect to enter into longer-term commercial supply agreements with key suppliers and manufacturers to fulfill and secure the ongoing and planned preclinical, clinical, and, if our product candidates are approved for marketing, our commercial supply needs for ourselves and our collaborators. Our long-term strategy is to secure at least two sources for the manufacturing of our products.

Manufacturing of any product candidate is subject to extensive regulations that impose various procedural and documentation requirements, which govern recordkeeping, manufacturing processes and controls, personnel, quality control and quality assurance, among others. We expect that all of our contract manufacturing organizations will manufacture RTB101 under current Good Manufacturing Practice, or cGMP, conditions. cGMP is a regulatory standard for the production of pharmaceuticals to be used in humans.

Competition

We consider Navitor Pharmaceuticals, Inc., or Navitor, to be our most direct competitor in developing novel therapeutics targeting TORC1 for aging-related diseases. However, Navitor's clinical TORC1 candidate is a TORC1 activator that is in Phase 1 clinical trials for treatment-resistant depression. We are aware of multiple other allosteric and catalytic mTOR inhibitors in development by other companies. We are not aware of any TORC1 inhibitors with TORC1 selectivity comparable to our product candidate, RTB101, being commercially developed.

We are also aware of other companies seeking to develop treatments to prevent or treat aging-related diseases through biological pathways unrelated to mTOR inhibition, including Calico Life Sciences LLC, or Calico, and UNITY Biotechnology, Inc., or Unity. Calico has not yet disclosed any pipeline candidates, and Unity's most advanced candidate, based on publicly disclosed information, is in Phase 1 clinical trials for osteoarthritis. Hence, we believe that we currently have the most clinically advanced program based on the stage of development of our competitors' programs.

We are aware of other companies that are potential competitors for prevention or treatment of respiratory tract infections. Companies pursuing broad-spectrum prophylactic and therapeutic treatments in respiratory tract infections include PrEP BioPharm, Inc. and Ena Therapeutics, Inc. (formerly Innavac). Based on publicly disclosed information, we believe that we have the most clinically advanced program, and the only program based on TORC1 selectivity. Narrow-spectrum prophylactic treatments are also being developed by potential competitors. Several of these treatments target the respiratory syncytial virus, or RSV, one of the top known causes of RTIs in older adults. However, as RTIs in the elderly are largely caused by many different viruses, we believe that our approach may be more broadly applicable in addressing RTIs.

Drug development is highly competitive and subject to rapid and significant technological advancements. Our ability to compete will significantly depend upon our ability to complete necessary clinical trials and regulatory approval processes, and effectively market any drug that we may successfully develop. Our current and potential future competitors may include pharmaceutical and biotechnology companies, academic institutions and government agencies. The primary competitive factors that will affect the commercial success of any product candidate for which we may receive regulatory approval include efficacy, safety and tolerability profile, dosing convenience, price, formulary coverage and reimbursement. Our existing or potential future competitors may have substantially greater financial, technical and human resources than we do and significantly greater experience in the discovery and development of product candidates, as well as in obtaining regulatory approvals of those product candidates in the United States and in foreign countries. Our current and potential future competitors may also have significantly more experience commercializing drugs that have been approved for marketing. Mergers and acquisitions in the pharmaceutical and biotechnology industries could result in even more resources being concentrated among a small number of our competitors.

Accordingly, our competitors may be more successful than us in obtaining regulatory approval for therapies and in achieving widespread market acceptance of their drugs. It is also possible that the development of a more effective treatment method for prevention of respiratory tract infections by a competitor could render our product candidate non-competitive or obsolete or reduce the demand for our product candidate before we can recover our development and commercialization expenses.

Government Regulation

Government authorities in the United States, at the federal, state and local level, and in other countries and jurisdictions, including the European Union, extensively regulate, among other things, the research, development, testing, manufacture, quality control, approval, packaging, storage, recordkeeping, labeling, advertising, promotion, distribution, marketing, post-approval monitoring and reporting, and import and export of pharmaceutical products. The processes for obtaining regulatory approvals in the United States and in foreign countries and jurisdictions, along with subsequent compliance with applicable statutes and regulations and other regulatory authorities, require the expenditure of substantial time and financial resources.

Review and Approval of Drugs in the United States

In the United States, the FDA regulates drugs primarily under the Federal Food, Drug, and Cosmetic Act, or FDCA, and its implementing regulations. The failure to comply with applicable U.S. requirements at any time during the product development process, approval process or after approval may subject an applicant and/or sponsor to a variety of administrative or judicial sanctions, including refusal by the FDA to approve pending applications, withdrawal of an approval, imposition of a clinical hold, issuance of warning letters and other types of letters, product seizures, total or partial suspension of production or distribution, injunctions, fines, refusals of government contracts, restitution, disgorgement of profits, or civil or criminal investigations and penalties brought by the FDA and the Department of Justice or other governmental entities. In addition, an applicant may need to recall a product.

An applicant seeking approval to market and distribute a new drug product in the United States must typically undertake the following:

- completion of nonclinical, or preclinical, laboratory tests, animal studies and formulation studies in compliance with the FDA's good laboratory practice, or GLP, regulations;
- submission to the FDA of an IND, which must take effect 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 at that site;
- performance of adequate and well-controlled human clinical trials in accordance with good clinical practices, or GCP, to establish the safety and efficacy of the proposed drug product for each indication;
- preparation and submission to the FDA of a new drug application, or NDA, and payment of user fees;
- review of the product by an FDA advisory committee, where appropriate or if applicable;

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

- satisfactory completion of FDA audits of clinical trial sites to assure compliance with GCPs and the integrity of the clinical data;

- FDA review and approval of the NDA; and

- compliance with any post-approval requirements, including Risk Evaluation and Mitigation Strategies, or REMS, and post-approval studies required by the FDA.

Preclinical Studies

Before an applicant begins testing a compound in humans, the drug candidate enters the preclinical testing stage. Preclinical studies include laboratory evaluation of the purity and stability of the manufactured drug substance or active pharmaceutical ingredient and the formulated drug or drug product, as well as in vitro and animal studies to assess the safety and activity of the drug for initial testing in humans and to establish a rationale for therapeutic use. The conduct of preclinical studies is subject to federal regulations and requirements, including GLP regulations. The results of the preclinical tests, together with manufacturing information, analytical data, any available clinical data or literature and plans for clinical trials, among other things, are submitted to the FDA as part of an IND. Some long-term preclinical testing, such as animal tests of reproductive adverse events and carcinogenicity, may continue after the IND is submitted.

The IND and IRB Processes

An IND is an exemption from the FDCA that allows an unapproved drug to be shipped in interstate commerce for use in an investigational clinical trial and a request for FDA authorization to administer such investigational drug to humans. Such authorization must be secured prior to interstate shipment and administration of the investigational drug. In an IND, applicants must submit a protocol for each clinical trial and any subsequent protocol amendments. In addition, the results of the preclinical tests, manufacturing information, analytical data, any available clinical data or literature and plans for clinical trials, among other things, are submitted to the FDA as part of an IND. The FDA requires a 30-day waiting period after the filing of each IND before clinical trials may begin. At any time during this 30-day period, the FDA may raise concerns or questions about the conduct of the trials as outlined in the IND and impose a clinical hold. In this case, the IND sponsor and the FDA must resolve any outstanding concerns before clinical trials can begin.

Following commencement of a clinical trial under an IND, the FDA may also place a clinical hold or partial clinical hold on that trial. A clinical hold is an order issued by the FDA to the sponsor to delay a proposed clinical investigation or to suspend an ongoing investigation. A partial clinical hold is a delay or suspension of only part of the clinical work requested under the IND. No more than 30 days after imposition of a clinical hold or partial clinical hold, the FDA will provide the sponsor a written explanation of the basis for the hold.

Following issuance of a clinical hold or partial clinical hold, an investigation may only resume after the FDA has notified the sponsor that the investigation may proceed. The FDA will base that determination on information provided by the sponsor correcting the deficiencies previously cited or otherwise satisfying the FDA that the investigation can proceed.

A sponsor may choose, but is not required, to conduct a foreign clinical study under an IND. When a foreign clinical study is conducted under an IND, all FDA IND requirements must be met unless waived. When the foreign clinical study is not conducted under an IND, the sponsor who wishes to rely upon it in support of its NDA must ensure that the study is conducted in accordance with good clinical practice, or GCP, including review and approval by an independent ethics committee, or IEC, and informed consent from subjects. The GCP requirements are intended to help ensure the protection of human subjects enrolled in non-IND foreign clinical studies, as well as the quality and integrity of the resulting data. FDA must also be able to validate the data from the study through an on-site inspection if necessary.

In addition to the foregoing IND requirements, an IRB representing each institution participating in the clinical trial must review and approve the plan for any clinical trial before it commences at that institution, and the IRB must conduct continuing review of the study at least annually. The IRB must review and approve, among other things, the study protocol and informed consent information to be provided to study subjects. An IRB must operate in compliance with FDA

regulations. An IRB can suspend or terminate approval of a clinical trial at its institution, or an institution it represents, if the clinical trial is not being conducted in accordance with the IRB's requirements or if the product candidate has been associated with unexpected serious harm to patients.

Additionally, some trials are overseen by an independent group of qualified experts organized by the trial sponsor, known as a data safety monitoring board or committee. This group provides authorization for whether or not a trial may move forward at designated check points based on access that only the group maintains to available data from the study. Suspension or termination of development during any phase of clinical trials can occur if it is determined that the subjects or patients are being exposed to an unacceptable health risk. Other reasons for suspension or termination may be made by us based on evolving business objectives and/or competitive climate.

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

Human Clinical Trials in Support of an NDA

Clinical trials involve the administration of the investigational product to human subjects under the supervision of qualified investigators in accordance with GCP requirements, which include, among other things, the requirement that all research subjects provide their informed consent in writing before their participation in any clinical trial. Clinical trials are conducted under written study protocols detailing, among other things, the inclusion and exclusion criteria, the objectives of the study, the parameters to be used in monitoring safety and the effectiveness criteria to be evaluated.

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

- *Phase 1.* The drug is initially introduced into healthy human subjects or, in certain indications such as cancer, patients with the target disease or condition and tested for safety, dosage tolerance, absorption, metabolism, distribution, excretion and, if possible, to gain an early indication of its effectiveness and to determine optimal dosage.

- *Phase 2.* The drug is administered to a limited patient population 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.* The drug is administered to an expanded patient population, generally at geographically dispersed clinical trial sites, in well-controlled clinical trials to generate enough data to evaluate the efficacy and safety of the product for approval, to establish the overall risk-benefit profile of the product and to provide adequate information for the labeling of the product.

- *Phase 4.* Post-approval studies may be conducted after initial regulatory approval. These studies are used to gain additional experience from the treatment of patients in the intended therapeutic indication.

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

Concurrent with clinical trials, companies often complete additional animal studies and must also develop additional information about the chemistry and physical characteristics of the drug as well as finalize a process for manufacturing the product in commercial quantities in accordance with cGMP requirements. The manufacturing process must be capable of consistently producing quality batches of the drug candidate and, among other things, the applicant must develop methods for testing the identity, strength, quality, purity, and potency of the final drug. Additionally, appropriate

packaging must be selected and tested, and stability studies must be conducted to demonstrate that the drug candidate does not undergo unacceptable deterioration over its shelf life.

Review of an NDA by the FDA

Assuming successful completion of required clinical testing and other requirements, the results of the preclinical studies and clinical trials, together with detailed information relating to the product's chemistry, manufacture, controls and proposed labeling, among other things, are submitted to the FDA as part of an NDA requesting approval to market the drug product for one or more indications. Under federal law, the submission of most NDAs is additionally subject to an application user fee, currently exceeding $2.5 million in fiscal year 2019 for applications requiring clinical data, and an annual prescription drug program fee exceeding $309,000 in fiscal year 2019. These fees are typically increased annually. Certain exceptions and waivers are available for some of these fees, such as an exception from the application fee for drugs with orphan designation.

The FDA conducts a preliminary review of an NDA within 60 days of its receipt, before accepting the NDA for filing, to determine whether the application is sufficiently complete to permit substantive review. The FDA may request additional information rather than accept an NDA for filing. In this event, the application must be resubmitted with the additional information. The resubmitted application is also subject to review before the FDA accepts it for filing. Once the submission is accepted for filing, the FDA begins an in-depth substantive review. The FDA has agreed to specified performance goals in the review process of NDAs. Applications for drugs containing novel active moieties are meant to be reviewed within ten months from the date of filing, and applications for "priority review" products containing novel active moieties are meant to be reviewed within six months of filing. The review process may be extended by the FDA for three additional months to consider new information or clarification provided by the applicant to address an outstanding deficiency identified by the FDA following the original submission.

Before approving an NDA, the FDA typically will inspect the facility or facilities where the product is or will be manufactured. These pre-approval inspections may cover all facilities associated with an NDA submission, including drug component manufacturing (such as active pharmaceutical ingredients), finished drug product manufacturing, and control testing laboratories. The FDA will not approve an application unless it determines that the manufacturing processes and facilities are in compliance with cGMP requirements and adequate to assure consistent production of the product within required specifications.

In addition, as a condition of approval, the FDA may require an applicant to develop a REMS. REMS use risk minimization strategies beyond the professional labeling to ensure that the benefits of the product outweigh the potential risks. To determine whether a REMS is needed, the FDA will consider the size of the population likely to use the product, seriousness of the disease, expected benefit of the product, expected duration of treatment, seriousness of known or potential adverse events, and whether the product is a new molecular entity. REMS can include medication guides, physician communication plans for healthcare professionals, and elements to assure safe use, or ETASU. ETASU may include, but are not limited to, special training or certification for prescribing or dispensing, dispensing only under certain circumstances, special monitoring, and the use of patient registries. The FDA may require a REMS before approval or post-approval if it becomes aware of a serious risk associated with use of the product. The requirement for a REMS can materially affect the potential market and profitability of a product.

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

Fast Track, Breakthrough Therapy, and Priority Review

The FDA has a number of programs intended to facilitate and expedite development and review of new drugs if they are intended to address an unmet medical need in the treatment of a serious or life-threatening disease or condition. Three of these programs are referred to as fast track designation, breakthrough therapy designation, and priority review designation.

Specifically, the FDA may designate a product for Fast Track review if it is intended, whether alone or in combination with one or more other products, for the treatment of a serious or life-threatening disease or condition, and it demonstrates the potential to address unmet medical needs for such a disease or condition. For Fast Track products, sponsors may have greater interactions with the FDA and the FDA may initiate review of sections of a Fast Track product's application before the application is complete. This rolling review may be available if the FDA determines, after preliminary

evaluation of clinical data submitted by the sponsor, that a Fast Track product may be effective. The sponsor must also provide, and the FDA must approve, a schedule for the submission of the remaining information and the sponsor must pay applicable user fees. However, the FDA's time period goal for reviewing a Fast Track application does not begin until the last section of the application is submitted. In addition, the Fast Track designation may be withdrawn by the FDA if the FDA believes that the designation is no longer supported by data emerging in the clinical trial process.

Second, a product may be designated as a Breakthrough Therapy if it is intended, either alone or in combination with one or more other products, to treat a serious or life-threatening disease or condition and preliminary clinical evidence indicates that the product may demonstrate substantial improvement over existing therapies on one or more clinically significant endpoints, such as substantial treatment effects observed early in clinical development. The FDA may take certain actions with respect to Breakthrough Therapies, including holding meetings with the sponsor throughout the development process; providing timely advice to the product sponsor regarding development and approval; involving more senior staff in the review process; assigning a cross-disciplinary project lead for the review team; and taking other steps to design the clinical trials in an efficient manner.

Third, the FDA may designate a product for priority review if it is a product that treats a serious or life-threatening disease or condition and, if approved, would provide a significant improvement in safety or effectiveness. The FDA determines, on a case-by-case basis, whether the proposed product represents a significant improvement when compared with other available therapies. Significant improvement may be illustrated by evidence of increased effectiveness in the treatment of a condition, elimination or substantial reduction of a treatment-limiting product reaction, documented enhancement of patient compliance that may lead to improvement in serious outcomes, and evidence of safety and effectiveness in a new subpopulation. A priority designation is intended to direct overall attention and resources to the evaluation of such applications, and to shorten the FDA's goal for taking action on a marketing application from ten months to six months.

Accelerated Approval Pathway

The FDA may grant accelerated approval to a product for a serious or life-threatening condition that provides meaningful therapeutic advantage to patients over existing treatments based upon a determination that the product has an effect on a surrogate endpoint that is reasonably likely to predict clinical benefit or on an intermediate clinical endpoint that can be measured earlier than an effect on irreversible morbidity or mortality, or IMM, and that is reasonably likely to predict an effect on IMM or other clinical benefit, taking into account the severity, rarity, or prevalence of the condition and the availability or lack of alternative treatments. Products granted accelerated approval must meet the same statutory standards for safety and effectiveness as those granted traditional approval.

For the purposes of accelerated approval, a surrogate endpoint is a marker, such as a laboratory measurement, radiographic image, physical sign, or other measure that is thought to predict clinical benefit, but is not itself a measure of clinical benefit. Surrogate endpoints can often be measured more easily or more rapidly than clinical endpoints. An intermediate clinical endpoint is a measurement of a therapeutic effect that is considered reasonably likely to predict the clinical benefit of a product, such as an effect on IMM. The FDA has limited experience with accelerated approvals based on intermediate clinical endpoints, but has indicated that such endpoints generally may support accelerated approval where the therapeutic effect measured by the endpoint is not itself a clinical benefit and basis for traditional approval, if there is a basis for concluding that the therapeutic effect is reasonably likely to predict the ultimate clinical benefit of a product.

The accelerated approval pathway is most often used in settings in which the course of a disease is long and an extended period of time is required to measure the intended clinical benefit of a product, even if the effect on the surrogate or intermediate clinical endpoint occurs rapidly.

The accelerated approval pathway is usually contingent on a sponsor's agreement to conduct, in a diligent manner, additional post-approval confirmatory studies to verify and describe the product's clinical benefit. As a result, a product candidate approved on this basis is subject to rigorous post-marketing compliance requirements, including the completion of Phase 4 or post-approval clinical trials to confirm the effect on the clinical endpoint. Failure to conduct required post-approval studies, or confirm a clinical benefit during post-marketing studies, could result in the FDA's withdrawal of the approval and require the withdrawal of the product from the market on an expedited basis. All promotional materials for product candidates approved under accelerated regulations are subject to prior review by the FDA.

The FDA's Decision on an NDA

On the basis of the FDA's evaluation of the NDA and accompanying information, including the results of the inspection of the manufacturing facilities and select clinical trial sites, the FDA may issue an approval letter or a complete response letter. An approval letter authorizes commercial marketing of the product with specific prescribing information for specific indications. A complete response letter generally outlines the deficiencies in the submission and may require substantial additional testing or information in order for the FDA to reconsider the application. If and when those deficiencies have been addressed to the FDA's satisfaction in a resubmission of the NDA, the FDA will issue an approval letter. The FDA has committed to reviewing such resubmissions in two or six months depending on the type of information included. Even with submission of this additional information, the FDA ultimately may decide that the application does not satisfy the regulatory criteria for approval. If the FDA approves a product, it may limit the approved indications for use for the product, require that contraindications, warnings or precautions be included in the product labeling, require that post-approval studies, including Phase 4 clinical trials, be conducted to further assess the drug's safety or effectiveness after approval, require testing and surveillance programs to monitor the product after commercialization, or impose other conditions, including distribution restrictions or other risk management mechanisms, including REMS, which can materially affect the potential market and profitability of the product. The FDA may prevent or limit further marketing of a product based on the results of post-market studies or surveillance programs.

Post-Approval Requirements

Drugs manufactured or distributed pursuant to FDA approvals are subject to pervasive and continuing regulation by the FDA, including, among other things, requirements relating to recordkeeping, periodic reporting, product sampling and distribution, advertising and promotion and reporting of adverse experiences with the product. After approval, many changes to the approved product, such as adding new indications or other labeling claims, are subject to prior FDA review and approval. There also are annual program fee requirements for certain marketed products.

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

In addition, drug manufacturers and other entities involved in the manufacture and distribution of approved drugs are required to register their establishments with the FDA and state agencies and are subject to periodic unannounced inspections by the FDA and these state agencies for compliance with cGMP requirements. Changes to the manufacturing process are strictly regulated and often require prior FDA approval before being implemented. FDA regulations also require investigation and correction of any deviations from cGMP and impose reporting and documentation requirements upon the NDA holder and any third-party manufacturers that the NDA holder may decide to use. Accordingly, manufacturers must continue to expend time, money, and effort in the area of production and quality control to maintain cGMP compliance.

Once an approval is granted, the FDA may withdraw the approval if compliance with regulatory requirements and standards is not maintained or if problems occur after the product reaches the market. Later discovery of previously unknown problems with a product, including adverse events of unanticipated severity or frequency, or with manufacturing processes, or failure to comply with regulatory requirements, may result in revisions to the approved labeling to add new safety information; imposition of post-market studies or clinical trials to assess new safety risks; or imposition of distribution or other restrictions under a REMS program. Other potential consequences include, among other things:

- restrictions on the marketing or manufacturing of the product, complete withdrawal of the product from the market or voluntary product recalls;
- fines, warning or untitled letters or holds on post-approval clinical trials;
- refusal of the FDA to approve pending NDAs or supplements to approved NDAs, or suspension or revocation of product approvals;
- product seizure or detention, or refusal to permit the import or export of products; or
- injunctions or the imposition of civil or criminal penalties.

The FDA strictly regulates marketing, labeling, advertising and promotion of products that are placed on the market. Drugs generally may be promoted only for the approved indications and in accordance with the provisions of the approved label. The FDA and other agencies actively enforce the laws and regulations prohibiting the promotion of off-label uses, and a company that is found to have improperly promoted off-label uses may be subject to significant liability.

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

Hatch-Waxman Amendments

Section 505 of the FDCA describes three types of marketing applications that may be submitted to the FDA to request marketing authorization for a new drug. A Section 505(b)(1) NDA is an application that contains full reports of investigations of safety and efficacy. A 505(b)(2) NDA is an application that contains full reports of investigations of safety and efficacy but where at least some of the information required for approval comes from investigations that were not conducted by or for the applicant and for which the applicant has not obtained a right of reference or use from the person by or for whom the investigations were conducted. This regulatory pathway enables the applicant to rely, in part, on the FDA's prior findings of safety and efficacy for an existing product, or published literature, in support of its application. Section 505(j) establishes an abbreviated approval process for a generic version of approved drug products through the submission of an Abbreviated New Drug Application, or ANDA. An ANDA provides for marketing of a generic drug product that has the same active ingredients, dosage form, strength, route of administration, labeling, performance characteristics and intended use, among other things, to a previously approved product, known as a reference listed drug, or RLD. ANDAs are termed "abbreviated" because they are generally not required to include preclinical (animal) and clinical (human) data to establish safety and efficacy. Instead, generic applicants must scientifically demonstrate that their product is bioequivalent to, or performs in the same manner as, the innovator drug through in vitro, in vivo, or other testing. The generic version must deliver the same amount of active ingredients to the site of drug action in the same amount of time as the innovator drug and can often be substituted by pharmacists under prescriptions written for the reference listed drug.

Non-Patent Exclusivity

Under the Hatch-Waxman Amendments, the FDA may not approve (or in some cases accept) an ANDA or 505(b)(2) application until any applicable period of non-patent data exclusivity for the RLD has expired. The FDCA provides a period of five years of non-patent data exclusivity for a new drug containing a new chemical entity, or NCE. For the purposes of this provision, an NCE is a drug that contains no active moiety that has previously been approved by the FDA in any other NDA. An active moiety is the molecule or ion responsible for the physiological or pharmacological action of the drug substance. In cases where such NCE exclusivity has been granted, an ANDA may not be filed with the FDA until the expiration of five years unless the submission is accompanied by a Paragraph IV certification, which states the proposed generic drug will not infringe one or more of the already approved product's listed patents or that such patents are invalid or unenforceable, in which case the applicant may submit its application four years following the original product approval.

The FDCA also provides for a period of three years of exclusivity for non-NCE drugs if the NDA or a supplement to the NDA includes reports of one or more new clinical investigations, other than bioavailability or bioequivalence studies, that were conducted by or for the applicant and are essential to the approval of the application or supplement. This three-year exclusivity period often protects changes to a previously approved drug product, such as a new dosage form, route of administration, combination or indication, but it generally would not protect the original, unmodified product from generic competition. Unlike five-year NCE exclusivity, an award of three-year exclusivity does not block the FDA from accepting ANDAs seeking approval for generic or versions of the drug as of the date of approval of the original drug product; it only prevents FDA from approving such ANDAs.

Hatch-Waxman Patent Certification and the 30-Month Stay

In seeking approval of an NDA or a supplement thereto, NDA sponsors are required to list with the FDA each patent with claims that cover the applicant's product or an approved method of using the product. Upon approval, each of the patents listed by the NDA sponsor is published in the FDA's Approved Drug Products with Therapeutic Equivalence Evaluations, commonly known as the Orange Book. Upon submission of an ANDA or 505(b)(2) NDA, an applicant is required to certify to the FDA concerning any patents for the RLD required to be listed in the Orange Book that:

- no patent information on the drug product that is the subject of the application has been submitted to the FDA;
- such patent has expired;
- the date on which such patent expires; or
- such patent is invalid, unenforceable or will not be infringed upon by the manufacture, use, or sale of the drug product for which the application is submitted.

Generally, the ANDA or 505(b)(2) NDA cannot be approved until all listed patents have expired, except where the ANDA or 505(b)(2) NDA applicant is not seeking approval of a use covered by the patent or the ANDA or 505(b)(2) applicant challenges a listed patent through the last type of certification, also known as a paragraph IV certification. If an applicant indicates that it is not seeking approval of a method of use covered by a patent, that method of use will not delay approval of the ANDA or 505(b)(2). If the applicant otherwise does not challenge the listed patents, the ANDA or 505(b)(2) NDA application will not be approved until all of the listed patents claiming the referenced product have expired. If the ANDA or 505(b)(2) NDA applicant has provided a paragraph IV certification the applicant must send notice of the paragraph IV certification to the NDA and patent holders once the application has been accepted for filing by the FDA. The NDA and patent holders may then initiate a patent infringement lawsuit in response to the notice of the paragraph IV certification. If the paragraph IV certification is challenged by an NDA holder or the patent owner(s) asserts a patent challenge to the paragraph IV certification within 45 days of receiving the notice, the FDA may not approve that application until the earlier of 30 months from the receipt of the notice of the paragraph IV certification, the expiration of the patent, when the infringement case concerning each such patent was favorably decided in the applicant's favor or settled, or such shorter or longer period as may be ordered by a court. This prohibition is generally referred to as the 30-month stay. In instances where an ANDA or 505(b)(2) NDA applicant files a paragraph IV certification, the NDA holder or patent owner(s) regularly take action to trigger the 30-month stay, recognizing that the related patent litigation may take many months or years to resolve. Thus, approval of an ANDA or 505(b)(2) application could be delayed for a significant period of time depending on the patent certification the applicant makes and the reference drug sponsor's decision to initiate patent litigation. If the drug has NCE exclusivity and the ANDA or 505(b)(2) application is submitted four years after approval, the 30-month stay is extended so that it expires 7 ½ years after approval of the innovator drug, unless the patent expires or there is a decision in the infringement case that is favorable to the ANDA applicant before then.

Pediatric Studies and Exclusivity

Under the Pediatric Research Equity Act of 2003, as amended, an NDA or supplement thereto for a drug with certain innovative features (*e.g.*, new active ingredient, new indication, new dosage form) must contain data that are adequate to assess the safety and effectiveness of the drug product for the claimed indications in all relevant pediatric subpopulations, and to support dosing and administration for each pediatric subpopulation for which the product is safe and effective. With enactment of the Food and Drug Administration Safety and Innovation Act, or FDASIA, in 2012, sponsors must also submit pediatric study plans prior to the assessment data. Those plans must contain an outline of the proposed pediatric study or studies the applicant plans to conduct, including study objectives and design, any deferral or waiver requests, and other information required by regulation. The applicant, the FDA, and the FDA's internal review committee must then review the information submitted, consult with each other, and agree upon a final plan. The FDA or the applicant may request an amendment to the plan at any time.

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

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

Orphan Drug Designation and Exclusivity

Under the Orphan Drug Act, the FDA may designate a drug product as an "orphan drug" if it is intended to treat a rare disease or condition (generally meaning that it affects fewer than 200,000 individuals in the United States, or more in cases in which there is no reasonable expectation that the cost of developing and making a drug product available in the United States for treatment of the disease or condition will be recovered from sales of the product). A company must request orphan product designation before submitting an NDA. If the request is granted, the FDA will disclose the identity of the therapeutic agent and its potential use. Orphan product designation does not convey any advantage in or shorten the duration of the regulatory review and approval process.

If a product with orphan status receives the first FDA approval for the drug for the disease or condition for which it has such designation or for a select indication or use within the rare disease or condition for which it was designated, the product generally will receive orphan product exclusivity. Orphan product exclusivity means that the FDA may not approve any other applications for the same product for the same indication for seven years, except in certain limited circumstances. Competitors may receive approval of different products for the indication for which the orphan product has exclusivity and may obtain approval for the same product but for a different indication. If a drug or drug product designated as an orphan product ultimately receives regulatory approval for an indication broader than what was designated in its orphan product application, it may not be entitled to exclusivity.

Patent Term Restoration and Extension

A patent claiming a new drug product may be eligible for a limited patent term extension under the Hatch-Waxman Amendments, which permits a patent term restoration of up to five years for patent term lost during product development and the FDA regulatory review. The restoration period granted is typically one-half the time between the effective date of an IND and the submission date of an NDA, plus the time between the submission date of an NDA and the ultimate approval date. Patent term restoration cannot be used to extend the remaining term of a patent past a total of 14 years from the product's approval date. Only one patent applicable to an approved drug product is eligible for the extension, and the application for the extension must be submitted prior to the expiration of the patent in question and within 60 days of drug approval. A patent that covers multiple drugs for which approval is sought can only be extended in connection with one of the approvals. The U.S. Patent and Trademark Office reviews and approves the application for any patent term extension or restoration in consultation with the FDA.

Review and Approval of Medicinal Products in the European Union

In order to market any product outside of the United States, a company must also comply with numerous and varying regulatory requirements of other countries and jurisdictions regarding quality, safety and efficacy and governing, among other things, clinical trials, marketing authorization, commercial sales and distribution of products. Whether or not it obtains FDA approval for a product, an applicant will need to obtain the necessary approvals by the comparable foreign regulatory authorities before it can commence clinical trials or marketing of the product in those countries or jurisdictions. Specifically, the process governing approval of medicinal products in the European Union generally follows the same lines as in the United States. It entails satisfactory completion of preclinical studies and adequate and well-controlled clinical trials to establish the safety and efficacy of the product for each proposed indication. It also requires the submission to the relevant competent authorities of a marketing authorization application, or MAA, and granting of a marketing authorization by these authorities before the product can be marketed and sold in the European Union.

Clinical Trial Approval

The Clinical Trials Directive 2001/20/EC, the Directive 2005/28/EC on Good Clinical Practice, or GCP, and the related national implementing provisions of the individual EU Member States govern the system for the approval of clinical trials in the European Union. Under this system, an applicant must obtain prior approval from the competent national authority of the EU Member States in which the clinical trial is to be conducted. Furthermore, the applicant may only start a clinical trial at a specific study site after the competent ethics committee has issued a favorable opinion. The clinical trial application must be accompanied by, among other documents, an investigational medicinal product dossier (the Common Technical Document) with supporting information prescribed by Directive 2001/20/EC, Directive 2005/28/EC, where relevant the implementing national provisions of the individual EU Member States and further detailed in applicable guidance documents.

In April 2014, the new Clinical Trials Regulation, (EU) No 536/2014 (Clinical Trials Regulation) was adopted. The Regulation is anticipated to apply in 2019. The Clinical Trials Regulation will be directly applicable in all the EU Member States, repealing the current Clinical Trials Directive 2001/20/EC. Conduct of all clinical trials performed in the European Union will continue to be bound by currently applicable provisions until the new Clinical Trials Regulation becomes applicable. The extent to which ongoing clinical trials will be governed by the Clinical Trials Regulation will depend on when the Clinical Trials Regulation becomes applicable and on the duration of the individual clinical trial. If a clinical trial continues for more than three years from the day on which the Clinical Trials Regulation becomes applicable the Clinical Trials Regulation will at that time begin to apply to the clinical trial.

The new Clinical Trials Regulation aims to simplify and streamline the approval of clinical trials in the European Union. The main characteristics of the regulation include: a streamlined application procedure via a single entry point, the “EU portal”; a single set of documents to be prepared and submitted for the application as well as simplified reporting procedures for clinical trial sponsors; and a harmonized procedure for the assessment of applications for clinical trials, which is divided in two parts. Part I is assessed by the competent authorities of all EU Member States in which an application for authorization of a clinical trial has been submitted (Member States concerned). Part II is assessed separately by each Member State concerned. Strict deadlines have been established for the assessment of clinical trial applications. The role of the relevant ethics committees in the assessment procedure will continue to be governed by the national law of the concerned EU Member State. However, overall related timelines will be defined by the Clinical Trials Regulation.

Marketing Authorization

To obtain a marketing authorization for a product under European Union regulatory systems, an applicant must submit an MAA either under a centralized procedure administered by the European Medicines Agency, or EMA, or one of the procedures administered by competent authorities in the EU Member States (decentralized procedure or mutual recognition procedure). A marketing authorization may be granted only to an applicant established in the European Union. Regulation (EC) No 1901/2006 provides that prior to obtaining a marketing authorization in the European Union, applicants have to demonstrate compliance with all measures included in an EMA-approved Pediatric Investigation Plan, or PIP, covering all subsets of the pediatric population, unless the EMA has granted (1) a product-specific waiver, (2) a class waiver or (3) a deferral for one or more of the measures included in the PIP.

The centralized procedure provides for the grant of a single marketing authorization by the European Commission that is valid for all EU Member States and three of the four European Free Trade Association, or EFTA, States, Iceland, Liechtenstein and Norway. Pursuant to Regulation (EC) No 726/2004, the centralized procedure is compulsory for specific products, including for medicines produced by certain biotechnological processes, products designated as orphan medicinal products, advanced therapy products and products with a new active substance indicated for the treatment of certain diseases, including products for the treatment of HIV or AIDS, cancer, diabetes, neurodegenerative diseases, auto-immune and other immune dysfunctions and viral diseases. For products with a new active substance indicated for the treatment of other diseases and products that are a significant therapeutic, scientific or technical innovation and whose authorization would be in the interest of public health at EU level, the centralized procedure is optional.

Under the centralized procedure, the Committee for Medicinal Products for Human Use, or the CHMP, established at the EMA is responsible for conducting the initial assessment of a product. The CHMP is also responsible for several post-authorization and maintenance activities, such as the assessment of modifications or extensions to an existing marketing authorization. Under the centralized procedure in the European Union, the maximum timeframe for the evaluation of an MAA is 210 days, excluding clock stops, when additional information or written or oral explanation is to be provided by the applicant in response to questions of the CHMP. Accelerated evaluation might be granted by the CHMP in exceptional cases, when a medicinal product is of major interest from the point of view of public health and in particular from the viewpoint of therapeutic innovation. If the CHMP accepts such request, the time limit of 210 days will be reduced to 150 days, but it is

possible that the CHMP can revert to the standard time limit for the centralized procedure if it considers that it is no longer appropriate to conduct an accelerated assessment. At the end of this period, the CHMP provides a scientific opinion on whether or not a marketing authorization should be granted in relation to a medicinal product. Within 67 days from the date of the CHMP Opinion, the European Commission will adopt its final decision on the marketing authorization application.

Unlike the centralized authorization procedure, the decentralized marketing authorization procedure requires a separate application to, and leads to separate approval by, the competent authorities of each EU Member State in which the product is to be marketed. This application is identical to the application that would be submitted to the EMA for authorization through the centralized procedure. The reference EU Member State prepares a draft assessment and drafts of the related materials within 120 days after receipt of a valid application. The resulting assessment report is submitted to the concerned EU Member States who, within 90 days of receipt, must decide whether to approve the assessment report and related materials. If a concerned EU Member State cannot approve the assessment report and related materials due to concerns relating to a potential serious risk to public health, disputed elements may be referred to the European Commission, whose decision is binding on all EU Member States.

The mutual recognition procedure similarly is based on the acceptance by the competent authorities of the EU Member States of the marketing authorization of a medicinal product by the competent authorities of other EU Member States. The holder of a national marketing authorization may submit an application to the competent authority of an EU Member State requesting that this authority recognize the marketing authorization delivered by the competent authority of another EU Member State.

Regulatory Data Protection in the European Union

In the European Union, innovative medicinal products approved on the basis of a complete independent data package qualify for eight years of data exclusivity upon marketing authorization and an additional two years of market exclusivity pursuant to Directive 2001/83/EC. Regulation (EC) No 726/2004 repeats this entitlement for medicinal products authorized in accordance the centralized authorization procedure. Data exclusivity prevents applicants for authorization of generics of these innovative products from referencing the innovator's data to assess a generic (abbreviated) application for a period of eight years. During an additional two-year period of market exclusivity, a generic marketing authorization application can be submitted and authorized, and the innovator's data may be referenced, but no generic medicinal product can be placed on the European Union market until the expiration of the market exclusivity. The overall ten-year period will be extended to a maximum of 11 years if, during the first eight years of those ten years, the marketing authorization holder obtains an authorization for one or more new therapeutic indications which, during the scientific evaluation prior to their authorization, are held to bring a significant clinical benefit in comparison with existing therapies. Even if a compound is considered to be a new chemical entity so that the innovator gains the prescribed period of data exclusivity, another company nevertheless could also market another version of the product if such company obtained marketing authorization based on an MAA with a complete independent data package of pharmaceutical tests, preclinical tests and clinical trials.

Periods of Authorization and Renewals

A marketing authorization has an initial validity for five years in principle. The marketing authorization may be renewed after five years on the basis of a re-evaluation of the risk-benefit balance by the EMA or by the competent authority of the EU Member State. To this end, the marketing authorization holder must provide the EMA or the competent authority with a consolidated version of the file in respect of quality, safety and efficacy, including all variations introduced since the marketing authorization was granted, at least six months before the marketing authorization ceases to be valid. The European Commission or the competent authorities of the EU Member States may decide, on justified grounds relating to pharmacovigilance, to proceed with one further five-year period of marketing authorization. Once subsequently definitively renewed, the marketing authorization shall be valid for an unlimited period. Any authorization which is not followed by the actual placing of the medicinal product on the European Union market (in case of centralized procedure) or on the market of the authorizing EU Member State within three years after authorization ceases to be valid (the so-called sunset clause).

Regulatory Requirements after a Marketing Authorization has been Obtained

In case an authorization for a medicinal product in the European Union is obtained, the holder of the marketing authorization is required to comply with a range of requirements applicable to the manufacturing, marketing, promotion and sale of medicinal products. These include:

- Compliance with the European Union's stringent pharmacovigilance or safety reporting rules must be ensured. These rules can impose post-authorization studies and additional monitoring obligations.

- The manufacturing of authorized medicinal products, for which a separate manufacturer's license is mandatory, must also be conducted in strict compliance with the applicable European Union laws, regulations and guidance, including Directive 2001/83/EC, Directive 2003/94/EC, Regulation (EC) No 726/2004 and the European Commission Guidelines for Good Manufacturing Practice. These requirements include compliance with European Union cGMP standards when manufacturing medicinal products and active pharmaceutical ingredients, including the manufacture of active pharmaceutical ingredients outside of the European Union with the intention to import the active pharmaceutical ingredients into the European Union.

- The marketing and promotion of authorized drugs, including industry-sponsored continuing medical education and advertising directed toward the prescribers of drugs and/or the general public, are strictly regulated in the European Union notably under Directive 2001/83/EC, as amended, and EU Member State laws.

Brexit and the Regulatory Framework in the United Kingdom

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

Healthcare Law and Regulation

Healthcare providers and third-party payors play a primary role in the recommendation and prescription of drug products that are granted regulatory approval. Arrangements with providers, consultants, third-party payors and customers are subject to broadly applicable fraud and abuse, anti-kickback, false claims laws, reporting of payments to physicians and teaching hospitals and patient privacy laws and regulations and other healthcare laws and regulations that may constrain our business and/or financial arrangements. Restrictions under applicable federal and state healthcare laws and regulations, include the following:

- the federal Anti-Kickback Statute, which prohibits, among other things, persons and entities from knowingly and willfully soliciting, offering, paying, receiving or providing remuneration, directly or indirectly, in cash or in kind, to induce or reward either the referral of an individual for, or the purchase, order or recommendation of, any good or service, for which payment may be made, in whole or in part, under a federal healthcare program such as Medicare and Medicaid; a person or entity need not have actual knowledge of the federal Anti-Kickback Statute or specific intent to violate it in order to have committed a violation; in addition, the government may assert that a claim that includes 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;

- the federal civil and criminal false claims laws, including the civil False Claims Act, and civil monetary penalties laws, which prohibit individuals or entities from, among other things, knowingly presenting, or causing to be presented, to the federal government, claims for payment that are false, fictitious or fraudulent; knowingly making a false statement or record material to a false or fraudulent claim or obligation to pay or transmit money or property to the federal government; or knowingly concealing or knowingly and improperly avoiding or decreasing an obligation to pay money to the federal government;

- the federal Health Insurance Portability and Accountability Act of 1996, or HIPAA, which created additional federal criminal laws that prohibit, among other things, knowingly and willfully executing, or attempting to execute, a scheme to defraud any healthcare benefit program or knowingly and willfully falsifying, concealing or covering up a material fact or making any materially false statement in connection with the delivery of or payment for healthcare benefits, items or services; similar to the federal Anti-Kickback Statute, a person or entity does not need to have actual knowledge of the statute or specific intent to violate it in order to have committed a violation;

- HIPAA, as amended by the Health Information Technology for Economic and Clinical Health Act, and their respective implementing regulations, including the Final Omnibus Rule published in January 2013, which impose obligations, including mandatory contractual terms, with respect to safeguarding the privacy, security and transmission of individually identifiable health information;

- the federal transparency requirements known as the federal Physician Payments Sunshine Act, under the Patient Protection and Affordable Care Act, as amended by the Health Care Education Reconciliation Act, or the Affordable Care Act, which requires certain manufacturers of drugs, devices, biologics and medical supplies to report annually to the Centers for Medicare & Medicaid Services, or CMS, within the United States Department of Health and Human Services, information related to payments and other transfers of value made by that entity to physicians and teaching hospitals, as well as ownership and investment interests held by physicians and their immediate family members;

- analogous state and foreign laws and regulations, such as state anti-kickback and false claims laws, which may apply to healthcare items or services that are reimbursed by non-governmental third-party payors, including private insurers; and

- European Privacy Laws including the General Data Protection Regulation and the E-Privacy Directive (2002/58/EC), and the national laws implementing or supplementing each of them.

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 to requiring manufacturers to report information related to payments to physicians and other healthcare providers or marketing expenditures and pricing information. 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.

Additional Regulation

In addition to the foregoing, state and federal laws regarding environmental protection and hazardous substances, including the Occupational Safety and Health Act, the Resource Conservancy and Recovery Act and the Toxic Substances Control Act, all affect our business. These and other laws govern our use, handling and disposal of various biological, chemical and radioactive substances used in, and wastes generated by, our operations. If our operations result in contamination of the environment or expose individuals to hazardous substances, we could be liable for damages and governmental fines. We believe that we are in material compliance with applicable environmental laws and that continued compliance therewith will not have a material adverse effect on our business. We cannot predict, however, how changes in these laws may affect our future operations.

GDPR and EU Privacy Law Reform

In the EU, Regulation 2016/679, known as the General Data Protection Regulation, or GDPR, replaced the EU Data Protection Directive on May 25, 2018. The GDPR introduced new data protection requirements in the European Union, as well as potential fines for noncompliance of up to the greater of €20 million or 4% of annual global revenue. The regulation imposes numerous new requirements for the collection, use and disclosure of personal information, including: more stringent requirements relating to data subject consent; what information must be shared with data subjects regarding how their personal information is used; the obligation to notify regulators and affected individuals of personal data breaches; extensive new internal privacy governance obligations; and obligations to honor expanded rights of individuals in relation to their personal information (e.g., the right to access, correct and delete their data). In addition, the GDPR maintains the EU Data Protection Directive's restrictions on cross border data transfer. The GDPR increases the responsibility and liability of pharmaceutical companies in relation to processing personal data, and companies may be required to put in place additional mechanisms to ensure compliance with the new EU data protection rules. Further, Brexit has created uncertainty with regard to the status of the United Kingdom as an 'adequate country' for the purposes of data transfers outside the European Economic Area. In particular, it is unclear how data transfers to and from the United Kingdom will be regulated. These changes may require us to find alternative bases for the compliant transfer of personal data from the United Kingdom to the United States and we are monitoring developments in this area.

Pharmaceutical Insurance Coverage and Healthcare Reform

In the United States and markets in other countries, patients who are prescribed treatments for their conditions and providers performing the prescribed services generally rely on third-party payors to reimburse all or part of the associated healthcare costs. Thus, even if a product candidate is approved, sales of the product 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, the product. 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, also known as a formulary, which might not include all of the approved products for a particular indication.

In order to secure coverage and reimbursement for any product that might be approved for sale, a company may need to conduct expensive pharmacoeconomic studies in order 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. Additionally, companies may also need to provide discounts to purchasers, private health plans or government healthcare programs. Nonetheless, product candidates may not be considered medically necessary or cost effective. A decision by a third-party payor not to cover a product could reduce physician utilization once the product is approved and have a material adverse effect on sales, results of operations and financial condition. Additionally, a payor's decision to provide coverage for a product does not imply that an adequate reimbursement rate will be approved. Further, one payor's determination to provide coverage for a product does not assure that other payors will also provide coverage and reimbursement for the product, and the level of coverage and reimbursement can differ significantly from payor to payor.

The containment of healthcare costs has become a priority of federal, state and foreign governments, and the prices of products have been a focus in this effort. Governments have shown significant interest in implementing cost-containment programs, including price controls, restrictions on reimbursement and requirements for substitution of generic products. Adoption of price controls and cost-containment measures, and adoption of more restrictive policies in jurisdictions with existing controls and measures, could further limit a company's revenue generated from the sale of any approved products. Coverage policies and third-party reimbursement rates may change at any time. Even if favorable coverage and reimbursement status is attained for one or more products for which a company or its collaborators receive regulatory approval, less favorable coverage policies and reimbursement rates may be implemented in the future.

There have been a number of federal and state proposals during the last few years regarding the pricing of pharmaceutical products, limiting coverage and the amount of reimbursement for drugs and other medical products, government control and other changes to the healthcare system in the United States. For example, in March 2010, the United States Congress enacted the Affordable Care Act, which, among other things, includes changes to the coverage and payment for products under government health care programs. Among the provisions of the Affordable Care Act of importance to our potential product candidates are:

- an annual, nondeductible fee on any entity that manufactures or imports specified branded prescription drugs and biologic products, apportioned among these entities according to their market share in certain government healthcare programs;
- expansion of eligibility criteria for Medicaid programs by, among other things, allowing states to offer Medicaid coverage to certain individuals with income at or below 133% of the federal poverty level, thereby potentially increasing a manufacturer's Medicaid rebate liability;
- expanded manufacturers' rebate liability under the Medicaid Drug Rebate Program by increasing the minimum rebate for both branded and generic drugs and revising the definition of "average manufacturer price," or AMP, for calculating and reporting Medicaid drug rebates on outpatient prescription drug prices;
- addressed a new methodology by which rebates owed by manufacturers under the Medicaid Drug Rebate Program are calculated for drugs that are inhaled, infused, instilled, implanted or injected;
- expanded the types of entities eligible for the 340B drug discount program;
- established the Medicare Part D coverage gap discount program by requiring manufacturers to provide a point-of-sale-discount off the negotiated price of applicable brand drugs to eligible beneficiaries during their

coverage gap period as a condition for the manufacturers' outpatient drugs to be covered under Medicare Part D; and

- a new Patient-Centered Outcomes Research Institute to oversee, identify priorities in, and conduct comparative clinical effectiveness research, along with funding for such research.

On October 13, 2017, President Trump signed an Executive Order terminating the cost-sharing subsidies that reimburse insurers under the Affordable Care Act. Several state Attorneys General filed suit to stop the administration from terminating the subsidies, but their request for a restraining order was denied by a federal judge in California on October 25, 2017. Further, on June 14, 2018, the U.S. Court of Appeals for the Federal Circuit ruled that the federal government was not required to pay more than $12 billion in Affordable Care Act risk corridor payments to third-party payors argued. The effects of this gap in reimbursement on third-party payors, the viability of the Affordable Care Act marketplace, providers, and our business, are not yet known. In addition, CMS has recently proposed regulations that would give states greater flexibility in setting benchmarks for insurers in the individual and small group marketplaces, which may have the effect of relaxing the essential health benefits required under the Affordable Care Act for plans sold through such marketplaces. Lastly, on December 14, 2018, a U.S. District Court Judge in Texas ruled that the Affordable Care Act is unconstitutional in its entirety because the "individual mandate" was repealed by Congress as part of the Tax Cuts and Jobs Act. While such U.S. District Court Judge, as well as the Trump Administration and CMS, have stated that the ruling will have no immediate effect pending appeal of the decision, it is unclear how this decision, subsequent appeals, and other efforts to repeal and replace the Affordable Care Act will impact the Affordable Care Act.

Other legislative changes have been proposed and adopted in the United States since the Affordable Care Act was enacted. In August 2011, the Budget Control Act of 2011, among other things, included aggregate reductions of Medicare payments to providers of 2% per fiscal year, which went into effect in April 2013 and will remain in effect through 2027 unless additional Congressional action is taken. In January 2013, then-President Obama signed into law the American Taxpayer Relief Act of 2012, which, among other things, further reduced Medicare payments to several providers, including hospitals, imaging centers and cancer treatment centers, and increased the statute of limitations period for the government to recover overpayments to providers from three to five years. In addition, recently there has been heightened governmental scrutiny over the manner in which manufacturers set prices for their commercial products, which has resulted in several Congressional inquiries and proposed bills 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 pharmaceutical products. Individual states in the United States have also become increasingly active in passing legislation and implementing regulations designed to control pharmaceutical 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 the United States, ensuring coverage and adequate payment for a product also involves challenges. Pricing of prescription pharmaceuticals is subject to government control in many countries. Pricing negotiations with government authorities can extend well beyond the receipt of regulatory approval for a product and may require a clinical trial that compares the cost-effectiveness of a product to other available therapies. The conduct of such a clinical trial could be expensive and result in delays in commercialization.

In the European Union, pricing and reimbursement schemes vary widely from country to country. Some countries provide that products may be marketed only after a reimbursement price has been agreed. Some countries may require the completion of additional studies that compare the cost-effectiveness of a particular product candidate to currently available therapies or so-called health technology assessments, in order to obtain reimbursement or pricing approval. For example, the European Union provides options for its member states to restrict the range of products for which their national health insurance systems provide reimbursement and to control the prices of medicinal products for human use. European Union member states may approve a specific price for a product or it may instead adopt a system of direct or indirect controls on the profitability of the company placing the product on the market. Other member states allow companies to fix their own prices for products but monitor and control prescription volumes and issue guidance to physicians to limit prescriptions. Recently, many countries in the European Union have increased the amount of discounts required on pharmaceuticals and these efforts could continue as countries attempt to manage healthcare expenditures, especially in light of the severe fiscal and debt crises experienced by many countries in the European Union. The downward pressure on healthcare costs in general, particularly prescription products, has become intense. As a result, increasingly high barriers are being erected to the entry of new products. Political, economic and regulatory developments may further complicate pricing negotiations, and pricing negotiations may continue after reimbursement has been obtained. Reference pricing used by various European Union member states, and parallel trade, i.e., arbitrage between low-priced and high-priced member states, can further reduce prices. There can be no assurance that any country that has price controls or reimbursement limitations for pharmaceutical products will allow favorable reimbursement and pricing arrangements for any products, if approved in those countries.

Employees

As of March 15, 2019, we had twenty-one full-time employees, including a total of eleven employees with M.D. or Ph.D. degrees, and no part-time employees. Of our workforce, fourteen employees are directly engaged in research and development activities, and seven employees provide administrative, business and operations support. None of our employees are represented by labor unions or covered by collective bargaining agreements. We consider the relationship with our employees to be good. We also use outside consultants and contractors for limited engagements.

Facilities

In January 2018, we entered into a multi-year agreement to lease office space in Boston, Massachusetts under an operating lease agreement. We believe that this office is sufficient to meet our current needs and that suitable additional space will be available as and when needed.

Legal Proceedings

In the ordinary course of our business we may, from time to time, be involved in lawsuits, claims, and other legal proceedings related to contracts, employment arrangements, operating activities, intellectual property or other matters. While the outcome of any such proceedings cannot be predicted with certainty, as of the date of this Annual Report on Form 10-K, we were not party to any legal proceedings or claims that we would expect to have a material adverse impact on our financial position, results of operations or cash flow.

Corporate Information

We were incorporated under the laws of the State of Delaware in July 2016. Our principal offices are located at 500 Boylston Street, 12th floor, Boston, MA 02116, and our telephone number is (857) 315-5521. Our website address is www.restorbio.com. Our website and the information contained on, or that can be accessed through, the website will not be deemed to be incorporated by reference in, and are not considered part of, this Annual Report on Form 10-K. You should not rely on any such information in making your decision whether to purchase our common stock.

Available Information

We file annual, quarterly, and current reports, proxy statements, and other documents with the Securities and Exchange Commission (SEC) under the Securities Exchange Act of 1934, as amended (the Exchange Act). The SEC maintains an Internet website that contains reports, proxy and information statements, and other information regarding issuers, including us, that file electronically with the SEC. The public can obtain any documents that we file with the SEC at www.sec.gov.

Copies of each of our filings with the SEC on Form 10-K, Form 10-Q, and Form 8-K and all amendments to those reports, can be viewed and downloaded free of charge at our website, www.restorbio.com after the reports and amendments are electronically filed with, or otherwise furnished to, the SEC.

Our code of conduct, corporate governance guidelines and the charters of our Audit Committee, Compensation Committee, and Nominating and Corporate Governance Committee are available through our website at www.restorbio.com.

Item 1A. Risk Factors.

Investing in our common stock involves a high degree of risk. In evaluating the Company and our business, you should carefully consider the following risks and uncertainties, together with all other information in this Annual Report on Form 10-K, including our consolidated financial statements and related notes and "Management's Discussion and Analysis of Results of Operations and Financial Condition," as well as our other filings with the Securities and Exchange Commission, before investing in our common stock. Any of the risk factors we describe below could adversely affect our business, financial condition or results of operations. The market price of our common stock could decline if one or more of these risks or uncertainties actually occur, causing you to lose all or part of your investment in our common stock. The risks and uncertainties we describe below are not the only ones we face. Additional risks and uncertainties that we currently do not know about or that we currently believe to be immaterial may also impair our business. Certain statements below are forward-looking statements. See "Special Note Regarding Forward-Looking Statements and Industry Data" in this Annual Report on Form 10-K.

Risks Related to Our Financial Position and Need for Capital

We have incurred significant losses since our inception. We anticipate that we will continue to incur significant losses for the foreseeable future, and we may never achieve or maintain profitability.

We are a clinical-stage biopharmaceutical company with a limited operating history. Investment in biopharmaceutical product development is highly speculative because it entails substantial upfront capital expenditures and significant risk that any potential product candidate will fail to demonstrate adequate effect or an acceptable safety profile, gain regulatory approval and become commercially viable. We have no products approved for commercial sale and have not generated any revenue from product sales to date, and we will continue to incur significant research and development and other expenses related to our ongoing operations. As a result, we are not profitable and have incurred losses in each period since our inception in July 2016. We have devoted a majority of our financial resources and efforts to research and development, including preclinical studies and our clinical trials. Our financial condition and operating results, including net losses, may fluctuate significantly from quarter to quarter and year to year. Accordingly, you should not rely upon the results of any quarterly or annual periods as indications of future operating performance. Additionally, net losses and negative cash flows have had, and will continue to have, an adverse effect on our stockholders' equity and working capital. For the years ended December 31, 2018 and 2017, we reported a net loss of $37.6 million and $33.8 million, respectively. As of December 31, 2018, we had an accumulated deficit of $71.4 million for the two preceding fiscal years. We expect to continue to incur significant losses for the foreseeable future, and we expect these losses to increase as we continue our research and development of, and seek regulatory approvals for, RTB101, alone or in combination with a rapalog, such as everolimus or sirolimus, and other product candidates.

We anticipate that our expenses will increase substantially if and as we:

- continue to develop and conduct clinical trials for our lead product candidate, RTB101, alone or in combination with a rapalog, such as everolimus or sirolimus;
- initiate and continue research, preclinical and clinical development efforts for any current or future product candidates;
- seek to identify additional product candidates;
- seek regulatory approvals for RTB101, alone or in combination with a rapalog, such as everolimus or sirolimus, or any other product candidates that successfully complete clinical development, if any;
- establish sales, marketing, distribution, manufacturing, supply chain and other commercial infrastructure in the future to commercialize various products for which we may obtain regulatory approval, if any;
- require the manufacture of larger quantities of RTB101 alone or in fixed dose combination with a rapalog, such as everolimus or sirolimus, for clinical development and, potentially, commercialization;
- maintain, expand and protect our intellectual property portfolio;

- hire and retain additional personnel, such as clinical, quality control, scientific and commercial personnel;
- add operational, financial and management information systems and personnel, including personnel to support our product development and help us comply with our obligations as a public company;
- add equipment and physical infrastructure to support our research and development; and
- acquire or in-license other product candidates and technologies.

Our ability to become and remain profitable depends on our ability to generate revenue. We do not expect to generate significant revenue unless and until we are, or any future collaborator is, able to obtain regulatory approval for, and successfully commercialize, RTB101, alone or in combination with a rapalog, such as everolimus or sirolimus, or any other product candidates. Successful commercialization will require achievement of key milestones, including demonstrating safety and efficacy in clinical trials, obtaining regulatory, including marketing, approval for these product candidates, manufacturing, marketing and selling those products for which we, or any of our future collaborators, may obtain regulatory approval, satisfying any post-marketing requirements and obtaining reimbursement for our products from private insurance or government payors. Because of the uncertainties and risks associated with these activities, we are unable to accurately and precisely predict the timing and amount of revenues, the extent of any further losses or if or when we might achieve profitability. We and any future collaborators may never succeed in these activities and, even if we do, or any future collaborators do, we may never generate revenues that are large enough for us to achieve profitability. Even if we do achieve profitability, we may not be able to sustain or increase profitability on a quarterly or annual basis. Additionally, our expenses could increase if we are required by the U.S. Food and Drug Administration, or FDA, or any comparable foreign regulatory authority to perform studies in addition to those currently expected, or if there are any delays in completing our clinical trials or the development of any of our product candidates.

Our failure to become and remain profitable would depress the market price of our common stock and could impair our ability to raise capital, expand our business, diversify our product offerings or continue our operations. If we continue to suffer losses as we have in the past, investors may not receive any return on their investment and may lose their entire investment.

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

We were formed in July 2016 and commenced research and development operations in March 2017. Our operations to date have been limited to organizing, staffing and financing our company, raising capital, in-licensing our technology and conducting research and development activities for our product candidates. We have not yet demonstrated an ability to obtain regulatory approvals, manufacture a commercial-scale product, or arrange for a third party to do so on our behalf, or conduct sales and marketing activities necessary for successful product commercialization. Accordingly, you should consider our prospects in light of the costs, uncertainties, delays and difficulties frequently encountered by companies in clinical development, especially clinical-stage biopharmaceutical companies such as ours. 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 or a history of successfully developing and commercializing pharmaceutical products.

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

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

Our operations have required substantial amounts of cash since inception. Developing pharmaceutical products, including conducting preclinical studies and clinical trials, is a very time-consuming, expensive and uncertain process that takes years to complete. For the foreseeable future, we expect to continue to rely on additional financing to achieve our business objectives.

For the years ended December 31, 2018 and 2017, we used $35.5 million and $11.0 million, respectively, in net cash for our operating activities, of which a majority related to research and development activities. We expect our expenses to increase substantially in connection with our ongoing activities, particularly as we initiate new clinical trials of, initiate new research and preclinical development efforts for and seek regulatory approval for, RTB101, alone or in combination with a rapalog, such as everolimus or sirolimus, or any product candidates that we develop or acquire, if any. In addition, if we obtain regulatory approval for RTB101, alone or in combination with a rapalog, such as everolimus or sirolimus, or any other product candidates, we expect to incur significant commercialization expenses related to product sales, marketing, manufacturing and distribution. Some of these expenses may be incurred in advance of regulatory approval and could be substantial. Furthermore, we expect to incur significant additional costs associated with our continued operation as a public company. Accordingly, we will need to obtain substantial additional funding in connection with our continuing operations. If we are unable to raise capital when needed or on attractive terms, we may be forced to delay, reduce or eliminate our research and development programs or any future commercialization efforts.

We intend to use our existing cash, cash equivalents and marketable securities, to fund the development of RTB101, alone or in combination with a rapalog, such as everolimus or sirolimus, for RTIs and other indications, and of our TORC1 follow-on candidate and other pipeline candidates, and the remainder, if any, for working capital and general corporate purposes. We will be required to expend significant funds in order to advance the development of RTB101 alone or in combination with a rapalog, such as everolimus or sirolimus, as well as other product candidates we may seek to develop or acquire. In addition, while we may seek one or more collaborators for future development of RTB101 alone or in combination with a rapalog, such as everolimus or sirolimus, for one or more additional indications beyond immunosenescence or in geographies outside of the United States, Europe and key territories, we may not be able to enter into a collaboration for RTB101 or any other product candidates for such indications or in such geographies on suitable terms, on a timely basis or at all. In any event, our existing cash, cash equivalents, and marketable securities will not be sufficient to fund all of the efforts that we plan to undertake or to fund the completion of development of RTB101 alone or in combination with a rapalog, such as everolimus or sirolimus, including activities related to the development of RTB101, alone or in combination with a rapalog, such as everolimus or sirolimus, for RTIs and other indications, and the development of our TORC1 follow-on candidate and other pipeline candidates. Accordingly, we will be required to obtain substantial additional funding through public or private equity offerings, debt financings, collaborations and licensing arrangements or other sources.

We cannot be certain that additional funding will be available on acceptable terms, or at all. We have no committed source of additional capital and if we are unable to raise additional capital in sufficient amounts or on terms acceptable to us, we may have to significantly delay, scale back or discontinue the development or commercialization of our product candidates or other research and development initiatives. Any of our current or future license agreements may also be terminated if we are unable to meet the payment or other obligations under the agreements. We could be required to seek collaborators for product candidates at an earlier stage than otherwise would be desirable or on terms that are less favorable than might otherwise be available or relinquish or license on unfavorable terms our rights to product candidates in markets where we otherwise would seek to pursue development or commercialization ourselves.

We believe our existing cash, cash equivalents and marketable securities, will enable us to fund our operating expenses and capital expenditure requirements at least into the second quarter of 2020. Our estimate may prove to be wrong, and we could use our available capital resources sooner than we currently expect. Further, changing circumstances, some of which may be beyond our control, could cause us to consume capital significantly faster than we currently anticipate, and we may need to seek additional funds sooner than planned. Our future funding requirements, both short- and long-term, will depend on many factors, including:

- the scope, progress, timing, costs and results of clinical trials of, and research and preclinical development efforts for, RTB101, alone or in combination with a rapalog, such as everolimus or sirolimus, and any future product candidates;
- our ability to enter into, and the terms and timing of, any collaborations, licensing or other arrangements on favorable terms, if at all;
- the number of future product candidates that we pursue and their development requirements;
- the outcome, timing and costs of seeking regulatory approvals;

- if approved, the costs of commercialization activities for RTB101, alone or in combination with a rapalog, such as everolimus or sirolimus, or any other product candidate that receives regulatory approval to the extent such costs are not the responsibility of any future collaborators, including the costs and timing of establishing product sales, marketing, distribution and manufacturing capabilities;

- subject to receipt of regulatory approval, revenue, if any, received from commercial sales of RTB101, alone or in combination with a rapalog, such as everolimus or sirolimus, or any future product candidates;

- the extent to which we in-license or acquire rights to other products, product candidates or technologies;

- our headcount growth and associated costs as we expand our research and development and establish a commercial infrastructure;

- the amount and timing of any payments we may be required to make, or that we may receive, in connection with the licensing, filing, prosecution, defense and enforcement of any patents or other intellectual property rights, including milestone and royalty payments and patent prosecution fees that we are obligated to pay pursuant to our license agreement;

- the costs of preparing, filing and prosecuting patent applications, maintaining and protecting our intellectual property rights including enforcing and defending intellectual property related claims; and

- the costs of operating as a public company.

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

We expect our expenses to increase in connection with our planned operations. Unless and until we can generate a substantial amount of revenue from our product candidates, we expect to finance our future cash needs through public or private equity offerings, debt financings, collaborations, licensing arrangements or other sources, or any combination of the foregoing. In addition, we may seek additional capital due to favorable market conditions or strategic considerations, even if we believe that we have sufficient funds for our current or future operating plans.

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

If we raise additional funds through collaborations or marketing, distribution or licensing arrangements with third parties, we may have to relinquish valuable rights to our technologies, future revenue streams or product candidates or grant licenses on terms that may not be favorable to us. If we are unable to raise additional funds when needed, we may be required to delay, limit, reduce or terminate our product development or future commercialization efforts or grant rights to develop and market product candidates that we would otherwise prefer to develop and market ourselves.

Changes in tax law, including the recently passed comprehensive tax reform bill, could adversely affect our business and financial condition.

The rules dealing with U.S. federal, state, and local income taxation are constantly under review by persons involved in the legislative process and by the Internal Revenue Service and the U.S. Treasury Department. Changes to tax laws (which changes may have retroactive application) could adversely affect us or holders of our common stock. In recent years, many such changes have been made and changes are likely to continue to occur in the future. For example, the Tax Cuts and Jobs Act, or the TCJA, was enacted in 2017 and significantly reforms the Internal Revenue Code of 1986, as amended, or the Code. The TCJA, 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 net 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, in each case, for losses generated after December 31, 2017 (though any such net operating losses may be carried forward indefinitely), and modifying or repealing many business deductions and credits (including reducing the business tax credit for certain clinical testing expenses incurred in the testing of certain drugs for rare diseases or conditions generally referred to as "orphan drugs"). We continue to examine the impact this tax reform legislation may have on our business.

Our ability to use net operating losses and research and development credits to offset future taxable income may be subject to certain limitations.

As of December 31, 2018, we had federal and state net operating loss carryforwards of $47.3 million and $49.4 million, respectively, which begin to expire in various amounts in 2036 (other than federal net operating loss carryforwards generated after December 31, 2017, which are not subject to expiration). As of December 31, 2018, we also had federal research and development tax credit carryforwards of $0.9 million, which begin to expire in 2037. These net operating loss and tax credit carryforwards could expire unused and be unavailable to offset future income tax liabilities. In addition, in general, under Sections 382 and 383 of the Internal Revenue Code of 1986, as amended, or the Code, a corporation that undergoes an "ownership change" is subject to limitations on its ability to utilize its pre-change net operating losses or tax credits, or NOLs or credits, to offset future taxable income or taxes. For these purposes, an ownership change generally occurs where the aggregate stock ownership of one or more stockholders or groups of stockholders who owns at least 5% of a corporation's stock increases its ownership by more than 50 percentage points over its lowest ownership percentage within a specified testing period. Our existing NOLs or credits may be subject to limitations arising from previous ownership changes. In addition, future changes in our stock ownership, many of which are outside of our control, could result in an ownership change under Sections 382 and 383 of the Code. Our NOLs or credits may also be impaired under state law. Accordingly, we may not be able to utilize a material portion of our NOLs or credits. We have not completed a study to determine whether our IPO and other transactions that have occurred over the past three years may have triggered an ownership change limitation. If we determine that an ownership change has occurred and our ability to use our historical NOLs or credits is materially limited, it would harm our future operating results by effectively increasing our future tax obligations.

Furthermore, our ability to utilize our NOLs or credits is conditioned upon our attaining profitability and generating U. S. federal and state taxable income. As described above under "Risk Factors—Risks Related to our Financial Position and Need for Additional Capital," we have incurred significant net losses since our inception and anticipate that we will continue to incur significant losses for the foreseeable future; and therefore, we do not know whether or when we will generate the U.S. federal or state taxable income necessary to utilize our NOL or credit carryforwards that are subject to limitation by Sections 382 and 383 of the Code.

Risks Related to the Discovery, Development and Commercialization of Our Product Candidates

Our business depends virtually entirely upon the success of RTB101 alone or in combination with a rapalog, such as everolimus or sirolimus. If we are unable to obtain regulatory approval for or successfully commercialize RTB101, alone or in combination with a rapalog, such as everolimus or sirolimus, our business may be materially harmed.

We currently have no products approved for sale and are investing the majority of our efforts and financial resources in the development of our lead product candidate, RTB101, either alone or in combination with a rapalog, such as everolimus or sirolimus. Successful continued development and ultimate regulatory approval of RTB101, alone or in combination with a rapalog, such as everolimus or sirolimus, for the treatment of aging-related diseases, including our lead indication, reducing the incidence of respiratory tract infections, or RTIs, is critical to the future success of our business. We will need to raise sufficient funds for, and successfully enroll and complete, our clinical development program for RTB101, alone or in combination with a rapalog, such as everolimus or sirolimus, to treat RTIs and possibly other aging-related diseases. The future regulatory and commercial success of this product candidate is subject to a number of risks, including the following:

- we may not have sufficient financial and other resources to initiate or complete the necessary clinical trials for RTB101, alone or in combination with a rapalog, such as everolimus or sirolimus;
- we may not be able to obtain adequate evidence of clinical efficacy and safety for RTB101, alone or in combination with a rapalog, such as everolimus or sirolimus, or to obtain regulatory approval of RTB101 for reducing the incidence of clinically symptomatic respiratory illness or other indications;

- even if RTB101 monotherapy succeeds in its clinical development and is approved for one or more targeted indications, there can be no assurance that RTB101 in combination with a rapalog, such as everolimus or sirolimus, would be developed successfully and approved, and vice versa;
- we may not be able to maintain an acceptable safety profile for RTB101 alone or in combination with a rapalog, such as everolimus or sirolimus, even if approved;
- we do not know the degree to which RTB101 alone or in combination with a rapalog, such as everolimus or sirolimus will have market uptake as a therapy by patients, the medical community or third-party payors, among others, if approved;
- in our clinical programs, we may experience variability in the response of subjects to treatment, the need to adjust clinical trial procedures and the need for additional clinical trial sites, which could delay our clinical trial progress;
- the results of our clinical trials may not meet the level of statistical significance required by the FDA, the European Medicines Agency, or EMA, or comparable foreign regulatory bodies for regulatory approval for reducing the incidence of clinically symptomatic respiratory illness or for other indications;
- we may have difficulty enrolling subjects in trials if, for instance, a current or future effective standard of care limits the desire of patients, physicians, or regulatory agencies to participate in or support clinical trials, or if patients choose to participate in the trials of other sponsors' product candidates;
- patients in our clinical trials may die or suffer other adverse effects for reasons that may or may not be related to RTB101, which could delay or prevent further clinical development;
- the requirements implemented by regulatory agencies may change at any time;
- the FDA, EMA or foreign regulatory agencies may require efficacy endpoints for a future clinical trial for reducing the incidence of respiratory illness that differ from the endpoints of our current or future trials, which may require us to conduct additional clinical trials;
- the mechanism of action of RTB101, alone or in combination with a rapalog, such as everolimus or sirolimus, is complex and we cannot guarantee the degree to which it will translate into a medical benefit in any indications;
- competitor products including generic products may be developed to reduce the incidence of clinically symptomatic respiratory illness that may have similar or better safety and efficacy or lower costs than RTB101 alone or in combination with a rapalog, such as everolimus or sirolimus;
- we may not be able to establish sales, marketing, distribution and other commercial infrastructure in the future to commercialize various products for which we may obtain regulatory approval;
- we or our contract manufacturers may not be able to manufacture RTB101, rapalogs, such as everolimus or sirolimus, the fixed dose combination of RTB101 with a rapalog, such as everolimus or sirolimus or other future product candidates at the appropriate quality or sufficient quantities to support further clinical development and/or commercialization;
- our investigational drug products or manufacturing processes may be considered by regulatory authorities, such as the FDA or EMA, to be unsuitable for continued development and/or commercialization;
- we may observe unexpected toxicities in preclinical safety or efficacy animal studies that delay, limit or prevent further clinical development;
- our intellectual property may not be patentable, valid or enforceable; and
- we may not be able to obtain, maintain, defend, protect or enforce our patents, our trade secrets, regulatory exclusivities and other intellectual property rights, both in the United States and internationally, including those that we have licensed under our license agreement with Novartis.

Many of these risks are beyond our control, including the risks related to clinical development, the regulatory submission process, potential threats to our intellectual property rights and the manufacturing, marketing and sales efforts of any future collaborator. If we are unable to develop, receive regulatory approval for, or successfully commercialize RTB101 alone or in combination with a rapalog, such as everolimus or sirolimus, or if we experience delays as a result of any of these risks or otherwise, our business could be materially harmed.

In addition, of the large number of drugs in development in the pharmaceutical industry, only a small percentage result in the submission of an NDA to the FDA and even fewer are approved for commercialization. Furthermore, even if we do receive regulatory approval for RTB101, alone or in combination with a rapalog, such as everolimus or sirolimus, any such approval may be subject to limitations on the indicated uses or patient populations for which we may market the product. Accordingly, even if we are able to obtain the requisite financing to continue to fund our development programs, we cannot assure you that we will successfully develop or commercialize RTB101, alone or in combination with a rapalog, such as everolimus or sirolimus, for RTIs or any other indications. If we or any of our future collaborators are unable to develop, or obtain regulatory approval for, or, if approved, successfully commercialize RTB101, alone or in combination with a rapalog, such as everolimus or sirolimus, for RTIs or any other indications, we may not be able to generate sufficient revenue to continue our business.

We have no experience as a company in obtaining regulatory approval for a drug.

As a company, we have never obtained regulatory approval for, or commercialized, a drug. It is possible that the FDA may refuse to accept any or all of our planned NDAs for substantive review or may conclude after review of our data that our application is insufficient to obtain regulatory approval for any current or future product candidates. If the FDA does not approve any of our planned NDAs, it may require that we conduct additional costly clinical, nonclinical or manufacturing validation studies before it will reconsider our applications. Depending on the extent of these or any other FDA-required studies, approval of any NDA or other application that we submit may be significantly delayed, possibly for several years, or may require us to expend more resources than we have available. Any failure or delay in obtaining regulatory approvals would prevent us from commercializing RTB101 alone or in combination with a rapalog, such as everolimus or sirolimus or any other product candidate, generating revenues and achieving and sustaining profitability. It is also possible that additional studies, if performed and completed, may not be considered sufficient by the FDA to approve any NDA or other application that we submit. If any of these outcomes occur, we may be forced to abandon the development of our product candidates, which would materially adversely affect our business and could potentially cause us to cease operations. We face similar risks for our applications in foreign jurisdictions.

We depend on the successful initiation and completion of clinical trials for RTB101 alone or in combination with a rapalog, such as everolimus or sirolimus. The positive clinical results, if any, obtained in prior or ongoing clinical trials may not be predictive of future results or repeated in later-stage clinical trials.

Before obtaining regulatory approval for the sale of RTB101, alone or in combination with a rapalog, such as everolimus or sirolimus, or any other potential product candidate, we must conduct additional clinical trials to demonstrate safety and efficacy in humans. The regulatory requirements for demonstrating efficacy and safety for obtaining approval for RTB101 alone or in combination with a rapalog such as everolimus or sirolimus may differ. We have not completed the clinical trials necessary to support an application for approval to market RTB101 alone or in combination with a rapalog, such as everolimus or sirolimus. Successful completion of such clinical trials is a prerequisite to submitting an NDA to the FDA and, consequently, the ultimate approval and commercial marketing of RTB101 alone or in combination with a rapalog, such as everolimus or sirolimus or any other potential product candidate. A failure of one or more clinical trials can occur at any stage of testing. We need to initiate and complete the requisite Phase 3 clinical trials prior to a submission for regulatory approval. We have conducted limited safety studies in humans to date and have only recently announced topline data from our Phase 2b clinical program to assess the safety, tolerability and efficacy of RTB101, alone or in combination with a rapalog, such as everolimus or sirolimus, in elderly patients. While we observed activity signals of RTB101 in this clinical trial in certain cohorts, not all cohorts that we investigated responded to RTB101 treatment, alone or in combination with a rapalog, such as everolimus or sirolimus. Additional toxicity and metabolism studies may be required by the FDA or other regulatory agencies. A number of companies in the pharmaceutical and biotechnology industries, including those with greater resources and experience than us, have suffered significant setbacks in late stage clinical development, even after seeing promising results in earlier clinical trials.

We may experience a number of unforeseen events during, or as a result of, clinical trials for RTB101, alone or in combination with a rapalog, such as everolimus or sirolimus, or any other potential product candidate that could adversely affect the costs, timing, or successful completion of our clinical trials, including:

- regulators or other comparable foreign regulatory authorities may disagree as to the design or implementation of our clinical trials;
- regulators, and/or institutional review boards or other reviewing bodies may not authorize us or our investigators to commence a clinical trial, or to conduct or continue a clinical trial at a prospective or specific 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 trial sites;
- clinical trials of RTB101, alone or in combination with a rapalog, such as everolimus or sirolimus, or any other potential product candidate may produce negative or inconclusive results, and we may decide, or regulators may require us, to conduct additional clinical trials or abandon product development programs;
- the number of subjects or patients required for clinical trials of RTB101, alone or in combination with a rapalog, such as everolimus or sirolimus, or any other potential product candidate may be larger than we anticipate, enrollment in these clinical trials may be insufficient or slower than we anticipate, and the number of clinical trials being conducted at any given time may be high and result in fewer available patients for any given clinical trial, or patients may drop out of these clinical trials at a higher rate than we anticipate;
- our third-party contractors, including those manufacturing our product candidates or conducting clinical trials on our behalf, may fail to comply with regulatory requirements or meet their contractual obligations to us in a timely manner, or at all;
- we might have to suspend or terminate clinical trials of RTB101, alone or in combination with a rapalog, such as everolimus or sirolimus, or any other potential product candidate for various reasons, including a finding that the subjects are being exposed to unacceptable health risks;
- we may have to amend clinical trial protocol submitted to regulatory authorities or conduct additional studies to reflect changes in regulatory requirements or guidance, which we may be required to resubmit to an Institutional Review Board, or IRB, and regulatory authorities for re-examination;
- regulators, institutional review boards or data monitoring committees may require or recommend that we or our investigators suspend or terminate clinical research for various reasons, including safety signals or noncompliance with regulatory requirements;
- the cost of clinical trials of RTB101, alone or in combination with a rapalog, such as everolimus or sirolimus, or any other potential product candidate may be greater than we anticipate;
- regulators, institutional review boards or other reviewing bodies may fail to approve or subsequently find fault with the manufacturing processes or facilities of third-party manufacturers with which we enter into agreement for clinical and commercial supplies, or the supply or quality of RTB101, rapalogs, such as everolimus or sirolimus or the fixed dose combination of RTB101 and a rapalog, such as everolimus or sirolimus or any other potential product candidate or other materials necessary to conduct clinical trials of our product candidates may be insufficient, inadequate or not available at an acceptable cost, or we may experience interruptions in supply;
- the potential for approval policies or regulations of the FDA or the applicable foreign regulatory agencies to significantly change in a manner rendering our clinical data insufficient for approval; and
- RTB101, alone or in combination with a rapalog, such as everolimus or sirolimus, or any other potential product candidate may have undesirable side effects or other unexpected characteristics.

Regulators, institutional review boards of the institutions in which clinical trials are being conducted or data monitoring committees may suspend or terminate a clinical trial due to a number of factors, including failure to conduct the clinical trial in accordance with regulatory requirements or our clinical protocols, inspection of the clinical trial operations or trial site by the FDA or other regulatory authorities resulting in the imposition of a clinical hold, unforeseen safety issues or adverse side effects, failure to demonstrate a benefit from using a drug, changes in governmental regulations or administrative actions or lack of adequate funding to continue the clinical trial.

Negative or inconclusive results from our clinical trials of RTB101 alone or in combination with a rapalog, such as everolimus or sirolimus, or any other clinical trial or preclinical studies in animals that we conduct, could mandate repeated or additional clinical trials. We do not know whether any clinical trials that we may conduct will demonstrate adequate efficacy and safety to result in regulatory approval to market RTB101, alone or in combination with a rapalog, such as everolimus or sirolimus, or any other potential product candidate. If later stage clinical trials do not produce favorable results, our ability to obtain regulatory approval for RTB101, alone or in combination with a rapalog, such as everolimus or sirolimus, or any other potential product candidate may be adversely impacted. For example, in a topline analysis of our Phase 2b clinical trial, we observed that treatment with RTB101 10 mg once daily resulted in a 30.6% decrease in the percentage of patients who developed one or more laboratory-confirmed RTIs as compared to placebo. No decrease was observed in the percentage of patients who developed one or more laboratory-confirmed RTIs in the RTB101 10 mg twice daily cohort or the combination therapy cohort, as compared to placebo. We conducted an end of Phase 2 meeting with the FDA in the first quarter of 2019.

Clinical trials must be conducted in accordance with the laws and regulations of the FDA, EMA and regulations and other applicable regulatory authorities' legal requirements, regulations or guidelines, and are subject to oversight by these governmental agencies and IRBs at the medical institutions where the clinical trials are conducted. In addition, clinical trials must be conducted with supplies of our product candidates produced under current good manufacturing practice, or cGMP, requirements and other regulations. Furthermore, we rely on CROs, and clinical trial sites to ensure the proper and timely conduct of our clinical trials and while we have agreements governing their committed activities, we have limited influence over their actual performance. We depend on our collaborators and on medical institutions and CROs to conduct our clinical trials in compliance with good clinical practice, or GCP, requirements. To the extent our collaborators or the CROs fail to enroll participants for our clinical trials, fail to conduct the study to GCP standards or are delayed for a significant time in the execution of trials, including achieving full enrollment, we may be affected by increased costs, program delays or both. In addition, clinical trials that are conducted in countries outside the United States and EU may subject us to further delays and expenses as a result of increased shipment costs, additional regulatory requirements and the engagement of non-U.S. and non-EU CROs, as well as expose us to risks associated with clinical investigators who are unknown to the FDA or the EMA, and different standards of diagnosis, screening and medical care.

We may be subject to additional risks because we are administering RTB101 in combination with other mTOR inhibitors, including rapalogs, such as everolimus or sirolimus.

We are evaluating RTB101 in combination with other mTOR inhibitors. The use of RTB101 in combination with other compounds may subject us to risks that we would not face if RTB101 were being administered as a monotherapy. For example, other mTOR inhibitors, including rapalogs such as everolimus or sirolimus, may have safety issues that are improperly attributed to RTB101 or the administration of RTB101 with such other therapies may result in safety issues that such other therapies or RTB101 would not have when used alone. In addition, other mTOR inhibitors with which we may administer RTB101, including a rapalog, such as everolimus or sirolimus, could be removed from the market and thus be unavailable for testing or commercial use concomitantly with RTB101. The outcome and cost of developing a product candidate to be used with other compounds is difficult to predict and dependent on a number of factors that are outside our reasonable control. If we experience efficacy or safety issues in our clinical trials in which RTB101 is being administered with a rapalog, such as everolimus or sirolimus, we may not receive regulatory approval for RTB101, which could prevent us from ever generating revenue or achieving profitability.

Competitive products may reduce or eliminate the commercial opportunity for RTB101, alone or in combination with a rapalog, such as everolimus or sirolimus. If our competitors develop technologies or product candidates more rapidly than we do, or their technologies are more effective or safer than ours, our ability to develop and successfully commercialize RTB101 alone or in combination with a rapalog, such as everolimus or sirolimus may be adversely affected.

The clinical and commercial landscape for aging-related diseases is highly competitive and subject to rapid and significant technological change. New data from competitors' product candidates continue to emerge. It is possible that these data may alter the current standard of care, completely precluding us from further developing RTB101, alone or in combination with a rapalog, such as everolimus or sirolimus, for RTIs or other aging-related diseases. Further, it is possible that we may initiate a clinical trial or trials for RTB101, alone or in combination with a rapalog, such as everolimus or

sirolimus, or any other potential product candidate only to find that data from competing products make it impossible for us to complete enrollment in clinical trials, resulting in our inability to submit applications for regulatory approval with regulatory agencies. Even if RTB101 were approved, alone or in combination with a rapalog, such as everolimus or sirolimus, it may have limited sales due to competition in the specific indications approved.

Competitive therapeutic treatments for aging-related diseases, including RTIs, include those that are currently in development and any new treatments that enter the market. We believe that a significant number of product candidates are currently under development, and may become commercially available in the future, for the treatment of conditions for which we may try to develop product candidates. Our potential competitors include large pharmaceutical and biotechnology companies, specialty pharmaceutical and generic drug companies, academic institutions, government agencies and research institutions. We consider Navitor Pharmaceuticals, Inc. to be our most direct competitor in developing novel therapeutics targeting the TORC1 mechanism of action. Additionally, we are also aware of other companies, including Calico Life Sciences LLC and UNITY Biotechnology, Inc., which are seeking to develop treatments to prevent or treat aging-related diseases through biological pathways that may be unrelated to mTOR inhibition. Similarly, there are several other companies, such as PrEP BioPharm, Inc., Virion Biotherapeutics, and Ena Therapeutics, Inc, which are pursuing broad-spectrum prophylactic and therapeutic treatments in RTIs.

Many of our competitors have greater financial, technical, manufacturing, marketing, sales and supply resources, and human resources or experience than us and significantly greater experience in the discovery and development of product candidates, obtaining FDA and other regulatory approvals of products and the commercialization of those products. Accordingly, our competitors may be more successful than we may be in obtaining regulatory approval for therapies and achieving widespread market acceptance. Our competitors' products may be more effective, or more effectively marketed and sold, than any product candidate we may commercialize and may render our therapies obsolete or non-competitive before we can recover development and commercialization expenses. If RTB101, alone or in combination with a rapalog, such as everolimus or sirolimus, is approved for the indications we are currently pursuing, it could compete with a range of therapeutic treatments that are in development. In addition, our competitors may succeed in developing, acquiring or licensing technologies and drug products that are more effective or less costly than RTB101 alone or in combination with a rapalog, such as everolimus or sirolimus or any other product candidates that we are currently developing or that we may develop, which could render our product candidates obsolete and noncompetitive.

If we obtain approval for RTB101, alone or in combination with a rapalog, such as everolimus or sirolimus, or any other future product candidate, we may face competition based on many different factors, including the efficacy, safety and tolerability of our products, the ease with which our products can be administered, the timing and scope of regulatory approvals for these products, the availability and cost of manufacturing, marketing and sales capabilities, price, reimbursement coverage and patent position. Existing and future competing products could present superior treatment alternatives, including being more effective, safer, less expensive or marketed and sold more effectively than any products we may develop. Competitive products may make any products we develop obsolete or noncompetitive before we recover the expense of developing and commercializing our product candidates. Such competitors could also recruit our employees, which could negatively impact our level of expertise and our ability to execute our business plan. Mergers and acquisitions in the pharmaceutical and biotechnology industries may result in even more resources being concentrated among a small number of competitors.

We also compete with other clinical stage companies and institutions for clinical trial participants, which could reduce our ability to recruit participants for our clinical trials. Delay in recruiting clinical trial participants could adversely affect our ability to bring a product to market prior to our competitors. Further, research and discoveries by others may result in breakthroughs that render our product candidates obsolete even before they begin to generate any revenue.

In addition, our competitors may obtain patent protection, regulatory exclusivities, or FDA approval and commercialize products more rapidly than we do, which may impact future approvals or sales of any of our product candidates that receive regulatory approval. If the FDA approves the commercial sale of RTB101, alone or in combination with a rapalog, such as everolimus or sirolimus, or any other product candidate, we will also be competing with respect to marketing capabilities and manufacturing efficiency. We expect competition among products will be based on product efficacy and safety, the timing and scope of regulatory approvals, availability of supply, marketing and sales capabilities, product price, reimbursement coverage by government and private third-party payors, regulatory exclusivities and patent position. Our profitability and financial position will suffer if our product candidates receive regulatory approval, but cannot compete effectively in the marketplace.

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

Furthermore, regulatory authorities' assessment of the data and results required to demonstrate safety and efficacy can change over time and can be affected by many factors, such as the emergence of new information, including on other products, changing policies and agency funding, staffing and leadership. We cannot be sure whether future changes to the regulatory environment will be favorable or unfavorable to our business prospects. For example, average review times at the FDA for regulatory approval applications can be affected by a variety of factors, including budget and funding levels and statutory, regulatory and policy changes.

The regulatory approval processes of the FDA, EMA and comparable foreign authorities are lengthy, time consuming and inherently unpredictable. If clinical trials of RTB101, alone or in combination with a rapalog, such as everolimus or sirolimus, fail to satisfactorily demonstrate safety and efficacy to the FDA or other regulators, or do not otherwise produce favorable results, we, or any future collaborators, may incur additional costs or experience delays in completing, or ultimately be unable to complete, the development and commercialization of RTB101 alone or in combination with a rapalog, such as everolimus or sirolimus.

We, and any future collaborators, are not permitted to commercialize, market, promote or sell any product candidate in the United States without obtaining regulatory approval from the FDA. Foreign regulatory authorities, such as the EMA, impose similar requirements. The time required to obtain approval by the FDA, EMA and comparable foreign authorities is unpredictable, but typically takes many years following the commencement of clinical trials and depends upon numerous factors, including substantial discretion of the regulatory authorities. In addition, approval policies, regulations, or the type and amount of clinical data necessary to gain approval may change during the course of a product candidate's clinical development and may vary among jurisdictions. To date, we have not submitted an NDA to the FDA or similar drug approval submissions to comparable foreign regulatory authorities for RTB101, alone or in combination with a rapalog, such as everolimus or sirolimus, or any other product candidate. We, and any future collaborators, must complete additional preclinical or nonclinical studies and clinical trials to demonstrate the safety and efficacy of our product candidates in humans before we will be able to obtain these approvals.

Clinical testing is expensive, difficult to design and implement, can take many years to complete and is inherently uncertain as to outcome. We cannot guarantee that any clinical trials will be conducted as planned or completed on schedule, if at all. The clinical development of RTB101 alone or in combination with a rapalog, such as everolimus or sirolimus or other drugs is susceptible to the risk of failure inherent at any stage of development, including failure to demonstrate efficacy in a clinical trial or across a broad population of patients, the occurrence of adverse events that are severe or medically or commercially unacceptable, failure to comply with protocols or applicable regulatory requirements, and determination by the FDA or any comparable foreign regulatory authority that a product candidate may not continue development or is not approvable. It is possible that even if RTB101, alone or in combination with a rapalog, such as everolimus or sirolimus, or any other product candidate has a beneficial effect, that effect will not be detected during clinical evaluation as a result of one or more of a variety of factors, including the seasonal and geographical RTI rates and size, duration, design, measurements, conduct or analysis of our clinical trials. Conversely, as a result of the same factors, our clinical trials may indicate an apparent positive effect of RTB101, alone or in combination with a rapalog, such as everolimus or sirolimus, or any other product candidate that is greater than the actual positive effect, if any. For example, in a topline analysis of our Phase 2b clinical trial, we observed that certain cohorts responded better to study drug treatment than others, and that certain cohorts did not respond at all. Similarly, in our clinical trials we may fail to detect toxicity of or intolerability caused by RTB101, everolimus or any other product candidate, or mistakenly believe that our product candidates are toxic or not well tolerated when that is not in fact the case.

Any inability to successfully complete preclinical and clinical development could result in additional costs to us, or any future collaborators. Moreover, if we, or any future collaborators, are required to conduct additional clinical trials or other testing of RTB101, alone or in combination with a rapalog, such as everolimus or sirolimus, or any other product candidate beyond the trials and testing that we or they contemplate, if we or they are unable to successfully complete clinical trials of our product candidates or other testing or the results of these trials or tests are unfavorable, uncertain or are only modestly favorable, or there are unacceptable safety concerns associated with our product candidates, we, or any future collaborators may:

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

Our failure to successfully initiate and complete clinical trials of RTB101, alone or in combination with a rapalog, such as everolimus or sirolimus, or any other product candidate and to demonstrate the efficacy and safety necessary to obtain regulatory approval to market RTB101, alone or in combination with a rapalog, such as everolimus or sirolimus, or any other product candidate would significantly harm our business. Our product candidate development costs will also increase if we experience delays in testing or regulatory approvals and we may be required to obtain additional funds to complete clinical trials. We cannot assure you that our clinical trials will begin as planned or be completed on schedule, if at all, or that we will not need to restructure our trials after they have begun. Significant clinical trial delays also could shorten any periods during which we may have the exclusive right to commercialize our product candidates or allow our competitors to bring products to market before we do and impair our ability to successfully commercialize our product candidates, which may harm our business and results of operations. In addition, many of the factors that cause, or lead to, delays of clinical trials may ultimately lead to the denial of regulatory approval of RTB101 alone or in combination with a rapalog, such as everolimus or sirolimus or any other product candidate.

Our product candidates may cause undesirable side effects or have other properties that could delay or prevent their regulatory approval, limit the commercial profile of an approved label, or result in significant negative consequences following regulatory approval, if obtained.

Undesirable side effects caused by RTB101, alone or in combination with a rapalog, such as everolimus or sirolimus, or any other product candidate could cause us or regulatory authorities to interrupt, delay or halt clinical trials and could result in a more restrictive label or the delay or denial of regulatory approval by the FDA or comparable foreign regulatory authorities. Results of our clinical trials could reveal a high and unacceptable severity and prevalence of side effects or unexpected characteristics. In clinical trials of RTB101, alone and in combination with everolimus, to date, there were no observed study drug-related serious adverse events in the Phase 2a clinical trial. In the Phase 2b clinical trial, 4.5% of subjects in the RTB101 10 mg once daily cohort had a serious adverse event, none of which were related to the study drug, though 4.5% of subjects in that arm discontinued the study drug due to an adverse event. The majority of observed study-drug related adverse events were mild or moderate in severity, transient and resolved without stopping the study drug. However, there can be no guarantee that we would observe a similar tolerability profile of RTB101, alone or in combination with a rapalog, such as everolimus or sirolimus, in future clinical trials. Many compounds that initially showed promise in clinical or earlier stage testing are later found to cause undesirable or unexpected side effects that prevented further development of the compound.

If unacceptable side effects arise in the development of our product candidates, we, the FDA or comparable foreign regulatory authorities, the IRBs, or independent ethics committees at the institutions in which our trials are conducted, or the Data Safety Monitoring Board, or DSMB, could suspend or terminate our clinical trials or the FDA or comparable foreign regulatory authorities could order us to cease clinical trials or deny approval of our product candidates for

any or all targeted indications. Treatment-emergent side effects that are deemed to be treatment-related could also affect subject recruitment or the ability of enrolled subjects to complete the trial or result in potential product liability claims. In addition, these side effects may not be appropriately recognized or managed by the treating medical staff. We expect to have to train medical personnel using our product candidates to understand the side effect profiles for our clinical trials and upon any commercialization of any of our product candidates. Inadequate training in recognizing or managing the potential side effects of our product candidates could result in patient injury or death. Any of these occurrences may harm our business, financial condition and prospects significantly.

Moreover, clinical trials of our product candidates are conducted in carefully defined sets of patients who have agreed to enter into clinical trials. Consequently, it is possible that our clinical trials, or those of any future collaborator, may indicate an apparent positive effect of a product candidate that is greater than the actual positive effect, if any, or alternatively fail to identify undesirable side effects. If, following approval of a product candidate, we, or others, discover that the product is less effective than previously believed or causes undesirable side effects that were not previously identified, any of the following adverse consequences could occur:

- regulatory authorities may withdraw their approval of the product, seize the product, or seek an injunction against its manufacture or distribution;
- we, or any future collaborators, may need to recall the product, or be required to change the way the product is administered or conduct additional clinical trials, or develop a surveillance program;
- additional restrictions may be imposed on the marketing of, or the manufacturing processes for, the particular product;
- regulatory authorities may require one or more post-market studies;
- regulatory authorities may impose distribution and/or use requirements, such as under a Risk Evaluation and Mitigation Strategy, or REMS;
- we may be subject to fines, injunctions or the imposition of civil or criminal penalties;
- regulatory authorities may require the addition of labeling statements, such as a “black box” warning or a contraindication, or issue safety alerts, Dear Healthcare Provider letters, press releases or other communications containing warnings or other safety information about the product;
- we, or any future collaborators, may be required to create a Medication Guide outlining the risks of the previously unidentified side effects for distribution to patients;
- we, or any future collaborators, could be sued and held liable for harm caused to patients;
- the product may become less competitive; and
- our reputation may suffer.

Any of these events could harm our business and operations and could negatively impact our stock price.

If we fail to develop and commercialize RTB101, alone or in combination with a rapalog, such as everolimus or sirolimus, for additional indications or fail to discover, develop and commercialize other product candidates, we may be unable to grow our business and our ability to achieve our strategic objectives would be impaired.

Although the development and commercialization of RTB101 for clinically symptomatic respiratory illness is our primary focus, as part of our longer-term growth strategy, we may evaluate RTB101, alone or in combination with a rapalog, such as everolimus or sirolimus, in other indications and develop other product candidates. We intend to evaluate internal opportunities from RTB101, alone or in combination with a rapalog, such as everolimus or sirolimus, or other product candidates from our TORC1 program, and also may choose to in-license or acquire other product candidates as well as commercial products to treat patients suffering from other disorders with significant unmet medical needs and limited treatment options. These other product candidates will require additional, time-consuming development efforts prior to

commercial sale, including preclinical studies, clinical trials and approval by the FDA and/or applicable foreign regulatory authorities. All product candidates are prone to the risks of failure that are inherent in pharmaceutical product development, including the possibility that the product candidate will not be shown to be sufficiently safe and effective for approval by regulatory authorities. In addition, we cannot assure you that any such products that are approved will be manufactured or produced economically, successfully commercialized or widely accepted in the marketplace or be more effective than other commercially available alternatives.

Research programs to identify 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;
- product candidates that 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; and
- a product candidate may not be accepted as safe and effective by patients, the medical community or third-party payors.

If we are unsuccessful in identifying and developing additional product candidates, our potential for growth and achieving our strategic objectives may be impaired.

Our preclinical programs may not produce new product candidates that are suitable for clinical trials or that can be successfully commercialized or generate revenue through collaborations.

We must successfully complete preclinical testing for our preclinical programs, including our TORC1 follow-on program, which may include demonstrating activity and comprehensive studies to show the lack of toxicity and other adverse effects in established animal models, before commencing clinical trials for any product candidate. Many pharmaceutical products do not successfully complete preclinical testing and, even if preclinical testing is successfully completed, may fail in clinical trials. In addition, there can be no assurance that positive results from preclinical studies will be predictive of results obtained from subsequent preclinical studies or clinical trials. Many pharmaceutical candidates are not suitable for manufacture on the scale or of the quality required for clinical trials or commercialization. Some pharmaceutical candidates that initially seem suitable may later be found to be insufficiently stable or may generate toxic impurities over time. We also cannot be certain that any product candidates that do advance into clinical trials will successfully demonstrate safety and efficacy in clinical trials. Even if we achieve positive results in early preclinical studies or clinical trials, they may not be predictive of the results in later trials.

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

Because we have limited financial and managerial resources, we intend to focus on developing product candidates for specific indications that we identify as most likely to succeed, in terms of both their potential for regulatory approval and commercialization. As a result, we may forego or delay pursuit of opportunities with other product candidates or for other indications that may prove to have greater commercial potential.

Our resource allocation decisions may cause us to fail to capitalize on viable commercial products or profitable market opportunities. Our spending on current and future research and development programs and product candidates for specific indications may not yield any commercially viable product candidates. If we do not accurately evaluate the commercial potential or target market for a particular product candidate, we may relinquish valuable rights to that product

candidate through collaboration, licensing or other royalty arrangements in cases in which it would have been more advantageous for us to retain sole development and commercialization rights to the product candidate.

If the FDA or comparable foreign regulatory authorities approve generic versions of RTB101, alone or in combination with a rapalog, such as everolimus or sirolimus, or any other product candidate of ours that receives regulatory approval, or such authorities do not grant our products appropriate periods of non-patent exclusivity before approving generic versions of such products, the sales of such products could be adversely affected.

Once an NDA is approved, the product covered thereby becomes a "listed drug" in the FDA's publication, "Approved Drug Products with Therapeutic Equivalence Evaluations," or the Orange Book. Manufacturers may seek approval of generic versions of reference listed drugs through submission of abbreviated new drug applications, or ANDAs, in the United States. In support of an ANDA, a generic manufacturer generally must show that its product has the same active ingredient(s), dosage form, strength, route of administration, conditions of use and labeling as the reference listed drug and that the generic version is bioequivalent to the reference listed drug, meaning, in part, that it is absorbed in the body at the same rate and to the same extent. Generic products may be significantly less costly to bring to market than the reference listed drug and companies that produce generic products are generally able to offer them at lower prices. Moreover, many states allow or require substitution of therapeutically equivalent generic drugs at the pharmacy level even if the branded drug is prescribed. Thus, following the introduction of a generic drug, a significant percentage of the sales of any branded product or reference listed drug may be lost to the generic product.

The FDA may not approve (or in some cases, accept) an ANDA for a generic product until any applicable period of non-patent exclusivity for the reference listed drug has expired. The Federal Food, Drug, and Cosmetic Act, or FDCA, provides a period of five years of non-patent exclusivity for a new drug containing a new chemical entity, or NCE. Specifically, in cases where such exclusivity has been granted, an ANDA may not be filed with the FDA until the expiration of five years unless the submission is accompanied by a Paragraph IV certification that a patent covering the listed drug is invalid, unenforceable or will not be infringed by the generic product, in which case the applicant may submit its application four years following approval of the listed drug. It is unclear whether the FDA will treat the active ingredients in our product candidates as NCEs and, therefore, afford them five years of NCE data exclusivity if they are approved. If any product we develop does not receive five years of NCE exclusivity, it may nevertheless receive three years of exclusivity if it meets applicable requirements. If so, the FDA may not approve generic versions of such product until three years after its date of approval. Three-year exclusivity is given to a drug if it contains an active moiety that has previously been approved, and the NDA includes reports of one or more new clinical investigations, other than bioavailability or bioequivalence studies, that were conducted by or for the applicant and are essential to the approval of the NDA. If approved, manufacturers may seek to launch these generic products following the expiration of the applicable marketing exclusivity period, even if we still have patent protection for our product.

Competition that our products, if approved, may face from generic versions of our products could negatively impact our future revenue, profitability and cash flows and substantially limit our ability to obtain a return on our investments in those product candidates.

If we encounter difficulties enrolling patients in our future clinical trials, our clinical development activities could be delayed or otherwise adversely affected.

We may experience difficulties in patient enrollment in our clinical trials for a variety of reasons. The timely completion of clinical trials in accordance with their protocols depends, among other things, on our ability to enroll a sufficient number of patients who remain in the study until its conclusion.

Patient enrollment is affected by many factors, including:

- the patient eligibility criteria defined in the protocol;
- the size of the patient population required for analysis of the trial's primary endpoints;
- the proximity of patients to study sites;
- the design of the trial;
- our ability to recruit clinical trial investigators with the appropriate competencies and experience;

- competing clinical trials and clinicians' and patients' perceptions as to the potential advantages and risks of the product candidate being studied in relation to other available therapies, including any new drugs that may be approved for the indications that we are investigating;

- our ability to obtain and maintain patient consents; and

- the risk that patients enrolled in clinical trials will drop out of the trials before completion.

In addition, our clinical trials will compete with other clinical trials for product candidates that are in the same therapeutic areas as our product candidates, and this competition will reduce the number and types of patients available to us, because some patients who might have opted to enroll in our trials may instead opt to enroll in a trial being conducted by one of our competitors. Since the number of qualified clinical investigators is limited, we expect to conduct some of our clinical trials at the same clinical trial sites that some of our competitors use, which will reduce the number of patients who are available for our clinical trials in such clinical trial site. In addition, because we intend to investigate our product candidates during the winter cold and flu season, this timing requirement may further limit the available pool of clinical trial subjects.

Our inability to enroll a sufficient number of patients for our clinical trials would result in significant delays or might require us to abandon one or more clinical trials altogether. Delays in patient enrollment may result in increased costs, affect the timing or outcome of the planned clinical trials, product candidate development and approval process and jeopardize our ability to seek and obtain the regulatory approval required to commence product sales and generate revenue, which could prevent completion of these trials, adversely affect our ability to advance the development of our product candidates, cause the value of our company to decline and limit our ability to obtain additional financing if needed.

Ingredients, excipients and other materials necessary to manufacture RTB101 or rapalogs, such as everolimus or sirolimus may not be available on commercially reasonable terms, or at all, which may adversely affect the development and commercialization of RTB101, alone or in combination with a rapalog, such as everolimus or sirolimus.

We and our third-party manufacturers must obtain from other third-party suppliers the active pharmaceutical ingredients, excipients and primary and secondary packaging materials necessary for our contract manufacturers to produce RTB101 or rapalogs, such as everolimus or sirolimus for our clinical trials and, to the extent approved or commercialized, for commercial distribution. There is no guarantee that we would be able to enter into all the necessary agreements with third-party suppliers that we require for the supply of such materials on commercially reasonable terms or at all. Even if we were able to secure such agreements or guarantees, our suppliers may be unable or choose not to provide us the ingredients, excipients or materials in a timely manner or in the quantities required. If we or our third-party manufacturers are unable to obtain the quantities of these ingredients, excipients or materials that are necessary for the manufacture of commercial supplies of RTB101 or rapalogs, such as everolimus or sirolimus, our ability to generate revenue from the sale of RTB101 alone or in combination with a rapalog, such as everolimus or sirolimus would be materially and adversely affected. Further, if we or our third-party manufacturers are unable to obtain active pharmaceutical ingredients, excipients and materials as necessary for our clinical trials or for the manufacture of commercial supplies of our product candidates, if approved, potential regulatory approval or commercialization would be delayed, which would materially and adversely affect our ability to generate revenue from the sale of our product candidates. As a result of these and other factors, the cost of manufacturing drug material may not support continued development or commercialization or may materially reduce revenue.

Even if RTB101, alone or in combination with a rapalog, such as everolimus or sirolimus, or any other product candidate of ours receives regulatory 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, in which case we may not generate significant revenues or become profitable.

We have never commercialized a product, and even if RTB101, alone or in combination with a rapalog, such as everolimus or sirolimus, or any other product candidate of ours is approved by the appropriate regulatory authorities for marketing and sale, it may nonetheless fail to gain sufficient market acceptance by physicians, patients, third-party payors and others in the medical community. The market for therapies targeting aging-related diseases with an immunotherapy is novel, and physicians may be reluctant to adopt novel therapies. In addition, patients and their physicians may not desire to add RTB101, alone or in combination with a rapalog, such as everolimus or sirolimus, even if approved, to their existing prophylactic treatment regime. For example, physicians are often reluctant to switch their patients from existing prophylactics for RTIs even when new and potentially more effective or convenient alternatives enter the market. Further, patients often acclimate to the treatment regime that they are currently taking and do not want to switch unless their physicians recommend switching products or they are required to switch due to lack of coverage and reimbursement. In addition, even if we are able to demonstrate our product candidates' safety and efficacy to the FDA and other regulators, safety or efficacy concerns in the medical community may hinder market acceptance.

Efforts to educate the medical community and third-party payors on the benefits of our product candidates may require significant resources, including management time and financial resources, and may not be successful. If RTB101, alone or in combination with a rapalog, such as everolimus or sirolimus, or any other product candidate is approved but does not achieve an adequate level of market acceptance, we may not generate significant revenues and we may not become profitable. The degree of market acceptance of our product candidates, if approved for commercial sale, will depend on a number of factors, including:

- the efficacy and safety of the product;
- the potential advantages of the product compared to competitive therapies;
- the prevalence and severity of any side effects;
- whether the product is recommended under physician prophylactic guidelines;
- whether the product is designated under physician treatment guidelines as a first-, second- or third-line therapy;
- our ability, or the ability of any future collaborators, to offer the product for sale at competitive prices;
- the product's convenience and ease of administration compared to alternative treatments;
- the willingness of the target patient population to try, and of physicians to prescribe, the product;
- limitations or warnings, including distribution or use restrictions contained in the product's approved labeling;
- the strength of sales, marketing and distribution support;
- changes in the standard of care for the targeted indications for the product; and
- availability and adequacy of coverage and reimbursement from government payors, managed care plans and other third-party payors.

Any failure by RTB101 alone or in combination with a rapalog, such as everolimus or sirolimus, or any other product candidate of ours that obtains regulatory approval to achieve market acceptance or commercial success would adversely affect our business prospects.

Even if we, or any future collaborators, are able to commercialize any product candidate that we, or they, develop, the product may become subject to unfavorable pricing regulations or third-party payor coverage and reimbursement policies, any of which could harm our business.

Patients who are provided medical treatment for their conditions generally rely on third party payors to reimburse all or part of the costs associated with their treatment. Therefore, our ability, and the ability of any future collaborators to commercialize any of our product candidates will depend in part on the extent to which coverage and reimbursement for these products and related treatments will be available from third-party payors including government health administration authorities and private health coverage insurers. Third-party payors decide which medications they will cover and establish reimbursement levels. We cannot be certain that coverage will be available and that reimbursement will be adequate for RTB101, alone or in combination with a rapalog, such as everolimus or sirolimus, or any of our other product candidates. Also, we cannot be certain that reimbursement policies will not reduce the demand for, or the price paid for, our products.

If coverage and reimbursement are not available, or reimbursement is available only to limited levels, we, or any future collaborators, may be limited in our ability to successfully commercialize our product candidates. Even if coverage is provided, the approved reimbursement amount may not be high enough to allow us, or any future collaborators, to establish or maintain pricing sufficient to realize a sufficient return on our or their investment. In the United States, no uniform policy of coverage and reimbursement for products exists among third-party payors and coverage and reimbursement for products can differ significantly from payor to payor. As a result, the coverage determination process is often a time-consuming and costly process that will require us to provide scientific and clinical support for the use of our products to each payor separately, with no assurance that coverage and adequate reimbursement will be applied consistently or obtained in the first instance.

There is significant uncertainty related to third-party payor coverage and reimbursement of newly approved drugs. Regulatory approvals, pricing and reimbursement for new drug products vary widely from country to country. Some countries require approval of the sale price of a drug before it can be marketed. In many countries, the pricing review period begins after marketing or product licensing approval is granted. In some foreign markets, prescription pharmaceutical pricing remains subject to continuing governmental control even after initial approval is granted. As a result, we, or any future collaborators, might obtain regulatory approval for a product in a particular country, but then be subject to price regulations that delay commercial launch of the product, which may negatively impact the revenues we are able to generate from the sale of the product in that country. Adverse pricing limitations may hinder our ability or the ability of any future collaborators to recoup our or their investment in one or more product candidates, even if our product candidates obtain regulatory approval.

The healthcare industry is acutely focused on cost containment, both in the United States and elsewhere. Government authorities and other third-party payors have attempted to control costs by limiting coverage and the amount of reimbursement for certain medications, which could affect our ability or that of any future collaborators to sell our product candidates profitably. These payors may not view our products, if any, as cost-effective, and coverage and reimbursement may not be available to our customers, or those of any future collaborators, or may not be sufficient to allow our products, if any, to be marketed on a competitive basis. Cost-control initiatives could cause us, or any future collaborators, to decrease the price we, or they, might establish for products, which could result in lower than anticipated product revenues. If the prices for our products, if any, decrease or if governmental and other third-party payors do not provide coverage or adequate reimbursement, our prospects for revenue and profitability will suffer.

There may also be delays in obtaining coverage and reimbursement for newly approved drugs, and coverage may be more limited than the indications for which the drug is approved by the FDA or comparable foreign regulatory authorities. Moreover, eligibility for reimbursement does not imply that any drug will be paid for in all cases or at a rate that covers our costs, including research, development, manufacture, sale and distribution. Reimbursement rates may vary, by way of example, according to the use of the product and the clinical setting in which it is used. Reimbursement rates may also be based on reimbursement levels already set for lower cost drugs or may be incorporated into existing payments for other services.

In addition, increasingly, third-party payors are requiring higher levels of evidence of the benefits and clinical outcomes of new technologies and are challenging prices. We cannot be sure that coverage will be available for any product candidate that we, or any future collaborator, commercialize and, if available, that the reimbursement rates will be adequate. Further, the net reimbursement for drug products may be subject to additional reductions if there are changes to laws that presently restrict imports of drugs from one country to another. An inability to promptly obtain coverage and adequate payment rates from both government-funded and private payors for any of our product candidates for which we, or any future collaborator, obtain regulatory approval could significantly harm our operating results, our ability to raise capital needed to commercialize products and our overall financial condition.

Product liability lawsuits against us or any of our future collaborators could divert our resources and attention, cause us to incur substantial liabilities and limit commercialization of our product candidates.

We are exposed to potential product liability and professional indemnity risks that are inherent in the research, development, manufacturing, marketing and use of pharmaceutical products. Currently, we have no products that have been approved for commercial sale; however, the current and future use of our product candidates by us and any collaborators in clinical trials, and the sale of these product candidates, if approved, in the future, may expose us to liability claims. We face an inherent risk of product liability lawsuits related to the use of our product candidates in elderly patients and will face an even greater risk if product candidates are approved by regulatory authorities and introduced commercially. Product liability claims may be brought against us or our partners by participants enrolled in our clinical trials, patients, health care providers, pharmaceutical companies, our collaborators or others using, administering or selling any of our future approved products. If we cannot successfully defend ourselves against any such claims, we may incur substantial liabilities or be required to limit commercialization of our product candidates. Regardless of the merits or eventual outcome, liability claims may result in:

- decreased demand for any of our future approved products;
- injury to our reputation;
- withdrawal of clinical trial participants;
- termination of clinical trial sites or entire trial programs;

- significant litigation costs;
- substantial monetary awards to, or costly settlements with, patients or other claimants;
- product recalls or a change in the indications for which they may be used;
- loss of revenue;
- diversion of management and scientific resources from our business operations; and
- the inability to commercialize our product candidates.

Although the clinical trial process is designed to identify and assess potential side effects, clinical development does not always fully characterize the safety and efficacy profile of a new medicine, and it is always possible that a drug, even after regulatory approval, may exhibit unforeseen side effects. If our product candidates were to cause adverse side effects during clinical trials or after approval, we may be exposed to substantial liabilities. Physicians and patients may not comply with any warnings that identify known potential adverse effects and patients who should not use our product candidates. If any of our product candidates are approved for commercial sale, we will be highly dependent upon consumer perceptions of us and the safety and quality of our products. We could be adversely affected if we are subject to negative publicity associated with illness or other adverse effects resulting from patients' use or misuse of our products or any similar products distributed by other companies.

Although we maintain product liability insurance coverage in the amount of up to $10.0 million in the aggregate, including clinical trial liability, this insurance may not fully cover potential liabilities that we may incur. The cost of any product liability litigation or other proceeding, even if resolved in our favor, could be substantial. We will need to increase our insurance coverage if we commercialize any product that receives regulatory approval. In addition, insurance coverage is becoming increasingly expensive. If we are unable to maintain sufficient insurance coverage at an acceptable cost or to otherwise protect against potential product liability claims, it could prevent or inhibit the development and commercial production and sale of our product candidates, which could harm our business, financial condition, results of operations and prospects.

We currently have limited marketing, sales or distribution infrastructure. If we are unable to develop our sales, marketing and distribution capability on our own or through collaborations with marketing partners, we will not be successful in commercializing our product candidates.

We currently have limited marketing, sales or distribution infrastructure. If RTB101 is approved for RTIs, we intend to establish a sales and marketing organization with technical expertise and supporting distribution capabilities to commercialize the approved product in key territories, which will require substantial additional resources. Some or all of these costs may be incurred in advance of any approval of RTB101, alone or in combination with a rapalog, such as everolimus or sirolimus. Any failure or delay in the development of our or third parties' internal sales, marketing and distribution capabilities would adversely impact the commercialization of RTB101, alone or in combination with a rapalog, such as everolimus or sirolimus, and other future product candidates.

Factors that may inhibit our efforts to commercialize our products on our own include:

- our inability to recruit and retain adequate numbers of effective sales and marketing personnel;
- the inability of sales personnel to obtain access to 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 relative to companies with more extensive product lines; and
- unforeseen costs and expenses associated with creating an independent sales and marketing organization.

With respect to our existing and future product candidates, we may choose to collaborate with third parties that have direct sales forces and established distribution systems to serve as an alternative to our own sales force and distribution systems. Our product revenue may be lower than if we directly marketed or sold our products, if approved. In addition, any revenue we receive will depend in whole or in part upon the efforts of these third parties, which may not be successful and are generally not within our control. If we are not successful in commercializing any approved products, our future product revenue will suffer, and we may incur significant additional losses.

If we do not establish sales and marketing capabilities successfully, either on our own or in collaboration with third parties, we will not be successful in commercializing our product candidates.

If we, or any future collaborators, experience any of a number of possible unforeseen events in connection with clinical trials of RTB101, alone or in combination with a rapalog, such as everolimus or sirolimus, or any other product candidate, potential clinical development, regulatory approval or commercialization of our product candidates could be delayed or prevented.

We, or any future collaborators, may experience numerous unforeseen events during, or as a result of, clinical trials that could delay or prevent clinical development, regulatory approval or commercialization of our product candidates, including:

- our product candidates may produce unfavorable or inconclusive results;
- regulators may require us or any future collaborators, to conduct additional clinical trials or abandon product development programs;
- the number of patients required for clinical trials of our product candidates may be larger than we, or any future collaborators anticipate, patient enrollment in these clinical trials may be slower than we, or any future collaborators, may anticipate or participants may drop out of these clinical trials at a higher rate than we, or any future collaborators, anticipate;
- the cost of planned clinical trials of our product candidates may be greater than we anticipate;
- our third-party contractors or those of any future collaborators, including those manufacturing our product candidates or components or ingredients thereof or conducting clinical trials on our behalf or on behalf of any future collaborators, may fail to comply with regulatory requirements or meet their contractual obligations to us or any future collaborators in a timely manner or at all;
- regulators, IRBs or independent ethics committees may not authorize us, any future collaborators or our or their investigators to commence a clinical trial or conduct a clinical trial at a prospective trial site;
- delays in reaching or failure to reach agreement on acceptable clinical trial contracts or clinical trial protocols with prospective trial sites;
- patients who enroll in a clinical trial may misrepresent their eligibility to do so or may otherwise not comply with the clinical trial protocol, resulting in the need to drop the patients from the clinical trial, increase the needed enrollment size for the clinical trial or extend the clinical trial’s duration;
- delay, suspension or termination of clinical trials of our product candidates for various reasons, including a finding that the participants are being exposed to unacceptable health risks, undesirable side effects or other unexpected characteristics of the product candidate; and
- regulators, IRBs or independent ethics committees may require that we, or any future collaborators, or our or their investigators suspend or terminate clinical research for various reasons, including noncompliance with regulatory requirements or their standards of conduct, a finding that the participants are being exposed to unacceptable health risks, undesirable side effects or other unexpected characteristics of the product candidate or findings of undesirable effects caused by a chemically or mechanistically similar product or product candidate.

Further, conducting clinical trials in foreign countries, as we have done and plan to do for our product candidates, presents additional risks that may delay completion of our clinical trials. These risks include the failure of enrolled patients in foreign countries to adhere to clinical protocol as a result of differences in healthcare services or cultural customs, managing additional administrative burdens associated with foreign regulatory schemes, as well as political and economic risks relevant to such foreign countries.

Product development costs for us, or any future collaborators, will increase if we, or they, experience delays in testing or pursuing regulatory approvals and we, or they, may be required to obtain additional funds to complete clinical trials and prepare for possible commercialization of our product candidates. We do not know whether any 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, or any future collaborators, may have the exclusive right to commercialize our product candidates or allow our competitors, or the competitors of any future collaborators, to bring products to market before we, or any future collaborators, do and impair our ability, or the ability of any future collaborators, to successfully commercialize our product candidates and may harm our business and results of operations. In addition, many of the factors that lead to clinical trial delays may ultimately lead to the denial of regulatory approval of any of our product candidates.

Results of preclinical studies and early clinical trials may not be predictive of results of future clinical trials, and such results do not guarantee approval of a product candidate by regulatory authorities.

The outcome of preclinical studies and early clinical trials may not be predictive of the success of later clinical trials, and interim results of clinical trials do not necessarily predict success in the results of completed clinical trials. Many companies in the pharmaceutical and biotechnology industries have suffered significant setbacks in late-stage clinical trials after achieving positive results in earlier development, and we could face similar setbacks. 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. In addition, preclinical and clinical data are often susceptible to varying interpretations and analyses. Many companies that believed their product candidates performed satisfactorily in preclinical studies and clinical trials have nonetheless failed to obtain regulatory approval for their product candidates. Even if we complete clinical development of RTB101 alone or in combination with a rapalog, such as everolimus or sirolimus for RTIs or any other indication, there can be no assurance that the FDA, EMA, or other regulatory authorities will approve RTB101 alone or in combination with a rapalog, such as everolimus or sirolimus for marketing.

In some instances, there can be significant variability in safety or efficacy results between different clinical trials of the same product candidate due to numerous factors, including changes in trial procedures set forth in protocols, differences in the size and type of the patient populations, changes in and adherence to the dosing regimen and other clinical trial procedures and the rate of dropout among clinical trial participants. If we fail to receive positive results in clinical trials of our product candidates, the development timeline and regulatory approval and commercialization prospects for our most advanced product candidate, and, correspondingly, our business and financial prospects would be negatively impacted.

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

Even if we complete the necessary preclinical studies and clinical trials, the regulatory approval process for product candidates is expensive, time consuming and uncertain and may prevent us or any future collaborators from obtaining approvals for the commercialization of RTB101 alone or in combination with a rapalog, such as everolimus or sirolimus or any other product candidate. As a result, we cannot predict when or if, and in which territories, we, or any future collaborators, will obtain regulatory approval to commercialize a product candidate.

The research, testing, manufacturing, labeling, approval, selling, marketing, promotion and distribution of products are subject to extensive regulation by the FDA and comparable foreign regulatory authorities. We, and any future collaborators, are not permitted to market RTB101, alone or in combination with a rapalog, such as everolimus or sirolimus, or any other product candidate in the United States or in other countries until we, or they, receive approval of an NDA from the FDA or regulatory approval from applicable regulatory authorities outside the United States. RTB101 is in clinical development and is subject to the risks of failure inherent in drug development. We have not submitted an application for or received regulatory approval for RTB101, alone or in combination with a rapalog, such as everolimus or sirolimus, or any other product candidate in the United States or in any other jurisdiction. We have limited experience in conducting and managing the clinical trials necessary to obtain regulatory approvals, including obtaining FDA approval of an NDA.

The process of obtaining regulatory approvals, both in the United States and abroad, is lengthy, expensive and uncertain. It 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 regulatory 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 regulatory approval also requires the submission of information about the product manufacturing process to, and inspection of manufacturing facilities by, the regulatory authorities. The FDA or other regulatory authorities may determine that RTB101, alone or in combination with a rapalog,

such as everolimus or sirolimus, or any other 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 regulatory approval or prevent or limit commercial use. Any regulatory 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 regulatory approval policies during the development period, changes in or the enactment or promulgation of additional statutes, regulations or guidance 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 are 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 regulatory approval of a product candidate. Any regulatory 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.

Moreover, principal investigators for our clinical trials may serve as scientific advisors or consultants to us from time to time and receive compensation in connection with such services. Under certain circumstances, we may be required to report some of these relationships to the FDA or other regulatory authority. The FDA or other regulatory authority may conclude that a financial relationship between us and a principal investigator has created a conflict of interest or otherwise affected interpretation of the study. The FDA or other regulatory authority may therefore question the integrity of the data generated at the applicable clinical trial site and the utility of the clinical trial itself may be jeopardized. This could result in a delay in approval, or rejection, of our marketing applications by the FDA or other regulatory authority, as the case may be, and may ultimately lead to the denial of regulatory approval of one or more of our product candidates.

Any delay in obtaining or failure to obtain required approvals could negatively impact our ability or that of any future collaborators to generate revenue from the particular product candidate, which likely would result in significant harm to our business and adversely impact our stock price.

Our failure to obtain regulatory approval in foreign jurisdictions would prevent our product candidates from being marketed abroad, and any approval we are granted for RTB101, alone or in combination with a rapalog, such as everolimus or sirolimus, or any of our other product candidates in the United States would not assure approval of product candidates in foreign jurisdictions.

In order to market any products outside of the United States, we must establish and comply with numerous and varying regulatory requirements of other countries regarding clinical trial design, safety and efficacy. Clinical trials conducted in one country may not be accepted by regulatory authorities in other countries, and regulatory approval in one country does not mean that regulatory approval will be obtained in any other country. Approval procedures vary among countries and can involve additional product testing and validation and additional administrative review periods. Seeking foreign regulatory approvals could result in significant delays, difficulties and costs for us and may require additional preclinical studies or clinical trials which would be costly and time consuming and could delay or prevent introduction of RTB101, alone or in combination with a rapalog, such as everolimus or sirolimus, or any of our other product candidates in those countries. We do not have experience in obtaining regulatory approval in international markets. If we or our partners fail to comply with regulatory requirements or to obtain and maintain required approvals, our target market will be reduced and our ability to realize the full market potential of our product candidates will be harmed.

The exit of the United Kingdom, or the UK, from the European Union, or the EU, may materially affect the regulatory regime that governs our handling of EU personal data and expose us to legal and business risks under European data privacy and protection law.

The UK's anticipated exit, or Brexit, from the EU on March 29, 2019 could add legal risk, uncertainty, complexity and cost to our handling of EU personal information and our privacy and data security compliance programs. It is possible that over time the UK Data Protection Act could become less aligned with the EU General Data Protection Regulation, or GDPR, which could require us to implement different compliance measures for the UK and the European Union and result in potentially enhanced compliance obligations for EU personal data. This risk would apply more immediately in the event of a "no-deal" Brexit (including no transition period).

In the event of a no-deal Brexit, it is highly unlikely that the European Commission, or EC, would grant an adequacy finding to the UK (a finding that the UK privacy legal framework provides an adequate level of privacy protection to EU individuals). Absent an adequacy finding, transfers of personal data from the EU to the UK would be illegal without adequate safeguards provided for under EC-approved mechanisms, such as current standard contractual clauses or, if approved in the future, an EU – UK privacy shield similar to the current framework in place between the EU and the U.S. The extensive authority of U.K. intelligence and law enforcement agencies, including to conduct surveillance on personal data flows, could reduce the likelihood that the EC would give the UK an adequacy finding, and reduce the likelihood that the EC would approve an EU – UK privacy shield. Accordingly, we would be exposed to legal risk for any of our EU-UK personal data transfers, including those that involve sensitive data such as patient and genetic data.

Even if we, or any future collaborators, obtain regulatory approvals for our product candidates, the terms of approvals and ongoing regulation of our products may limit how we manufacture and market our products, which could impair our ability to generate revenue.

Once regulatory approval has been granted, an approved product and its manufacturer and marketer are subject to ongoing review and extensive regulation. We, and any future collaborators, must therefore comply with requirements concerning advertising and promotion for any of our product candidates for which we or they obtain regulatory 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 and any future collaborators 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 current Good Manufacturing Practices, or cGMPs, which include requirements relating to quality control and quality assurance as well as the corresponding maintenance of records and documentation and reporting requirements. We, our contract manufacturers, any future collaborators and their contract manufacturers could be subject to periodic unannounced inspections by the FDA to monitor and ensure compliance with cGMPs. Despite our efforts to inspect and verify regulatory compliance, one or more of our third-party manufacturing vendors may be found on regulatory inspection by FDA or other authorities to be not in compliance with cGMP regulations, which may result in shutdown of the third-party vendor or invalidation of drug product lots or processes. In some cases, a product recall may be warranted or required, which would materially affect our ability to supply and market our drug products.

Accordingly, assuming we, or any future collaborators, receive regulatory approval for one or more of our product candidates, we, and any future collaborators, and our and their 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, and any future collaborators, are not able to comply with post-approval regulatory requirements, we, and any future collaborators, could have the regulatory approvals for our products withdrawn by regulatory authorities and our, or any future collaborators', ability to market any future products could be limited, which could adversely affect our ability to achieve or sustain profitability. Further, the cost of compliance with post-approval regulations may have a negative effect on our operating results and financial condition.

We are subject to extensive government regulation and the failure to comply with these regulations may have a material adverse effect on our operations and business.

Both before and after approval of any product, we and our suppliers, contract manufacturers and clinical investigators are subject to extensive regulation by governmental authorities in the United States and other countries, covering, among other things, testing, manufacturing, quality control, clinical trials, post-marketing studies, labeling, advertising, promotion, distribution, import and export, governmental pricing, price reporting and rebate requirements. Failure to comply with applicable requirements could result in one or more of the following actions: warning or untitled letters; unanticipated expenditures; delays in approval or refusal to approve a product candidate; voluntary product recall; product seizure; interruption of manufacturing or clinical trials; operating or marketing restrictions; injunctions; criminal prosecution and civil or criminal penalties including fines and other monetary penalties; exclusion from federal health care programs such as Medicare and Medicaid; adverse publicity; and disruptions to our business. Further, government investigations into potential violations of these laws would require us to expend considerable resources and face adverse publicity and the potential disruption of our business even if we are ultimately found not to have committed a violation.

Obtaining FDA approval of our product candidates requires substantial time, effort and financial resources and may be subject to both expected and unforeseen delays, and there can be no assurance that any approval will be granted for any of our product candidates on a timely basis, if at all. The FDA may decide that our data are insufficient for approval of our product candidates and require additional preclinical, clinical or other studies or additional work related to chemistry, manufacturing and controls. In addition, we, the FDA, IRBs or independent ethics committees may suspend or terminate human clinical trials at any time on various grounds, including a finding that the patients are or would be exposed to an unacceptable health risk or because of the way in which the investigators on which we rely carry out the trials. If we are required to conduct additional trials or to conduct other testing of our product candidates beyond that which we currently contemplate for regulatory approval, if we are unable to complete successfully our clinical trials or other testing, or if the results of these and other trials or tests fail to demonstrate efficacy or raise safety concerns, we may face substantial additional expenses, be delayed in obtaining regulatory approval for our product candidates or may never obtain regulatory approval.

We are also required to comply with extensive governmental regulatory requirements after a product has received marketing authorization. Governing regulatory authorities may require post-marketing studies that may negatively impact the commercial viability of a product. Once on the market, a product may become associated with previously undetected adverse effects and/or may experience manufacturing or other commercial difficulties. As a result of any of these or other problems, a product's regulatory approval could be withdrawn, suspended or modified which could harm our business and operating results.

Any of our product candidates for which we, or any future collaborators, obtain regulatory approval in the future will be subject to ongoing obligations and continued regulatory review, which may result in significant additional expense. If approved, our product candidates could be subject to post-marketing restrictions or withdrawal from the market and we, or any future collaborators, may be subject to substantial penalties if we, or they, fail to comply with regulatory requirements or if we, or they, experience unanticipated problems with our products following approval.

Any of our product candidates for which we, or any future collaborators, obtain regulatory approval, as well as the manufacturing processes, post-approval studies, labeling, advertising and promotional activities for such product, among other things, will be subject to ongoing requirements of and review by the FDA, EMA and other regulatory authorities. These requirements include submissions of safety and other post-marketing information and reports, registration and listing requirements, requirements relating to manufacturing, quality control, quality assurance and corresponding maintenance of records and documents, requirements regarding the distribution of samples to physicians and recordkeeping. We and our contract manufacturers will also be subject to user fees and periodic inspection by the FDA, EMA and other regulatory authorities to monitor compliance with these requirements and the terms of any product approval we may obtain. Even if regulatory approval of a product candidate is granted, the approval may be subject to limitations on the indicated uses for which the product may be marketed or to the conditions of approval, including the requirement to implement a REMS.

The FDA, EMA and other regulatory authorities may also impose requirements for costly post-marketing studies or clinical trials and surveillance to monitor the safety or efficacy of a product. The FDA and other agencies, including the Department of Justice, closely regulate and monitor the post-approval marketing and promotion of products to ensure that they are manufactured, marketed and distributed only for the approved indications and in accordance with the provisions of the approved labeling. The FDA imposes stringent restrictions on manufacturers' communications regarding off-label use and if we, or any future collaborators, do not market any of our product candidates for which we, or they, receive regulatory approval for only their approved indications, we, or they, may be subject to warnings or enforcement action for off-label marketing if it is alleged that we are doing so. Violation of the FDCA and other statutes relating to the promotion and advertising of prescription drugs may lead to investigations or allegations of violations of federal and state health care fraud and abuse laws and state consumer protection laws, including the False Claims Act.

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

- restrictions on the manufacturing of such products;
- restrictions on the labeling or marketing of such products;
- restrictions on product distribution or use;

- requirements to conduct post-marketing studies or clinical trials;
- warning letters 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;
- restrictions on coverage by third-party payors;
- fines, restitution or disgorgement of profits or revenues;
- exclusion from federal health care programs such as Medicare and Medicaid;
- suspension or withdrawal of regulatory approvals;
- refusal to permit the import or export of products;
- product seizure; or
- injunctions or the imposition of civil or criminal penalties.

The efforts of the Administration to pursue regulatory reform may limit FDA's ability to engage in oversight and implementation activities in the normal course, and that could negatively impact our business.

The policies of the FDA and of other regulatory authorities may change and additional government regulations may be enacted that could prevent, limit or delay regulatory approval of our product candidates. We cannot predict the likelihood, nature or extent of government regulation that may arise from future legislation or administrative or executive action, either in the United States or abroad. For example, certain policies of the current administration may impact our business and industry. Namely, the current administration has taken several executive actions, including the issuance of a number of executive orders, that could impose significant burdens on, or otherwise materially delay, the FDA's ability to engage in routine regulatory and oversight activities such as implementing statutes through rulemaking, issuance of guidance, and review and approval of marketing applications. On January 30, 2017, President Trump issued an executive order, applicable to all executive agencies, including the FDA, that requires that for each notice of proposed rulemaking or final regulation to be issued in fiscal year 2017, the agency shall identify at least two existing regulations to be repealed, unless prohibited by law. These requirements are referred to as the "two-for-one" provisions. This executive order includes a budget neutrality provision that requires the total incremental cost of all new regulations in the 2017 fiscal year, including repealed regulations, to be no greater than zero, except in limited circumstances. For fiscal years 2018 and beyond, the executive order requires agencies to identify regulations to offset any incremental cost of a new regulation. In interim guidance issued by the Office of Information and Regulatory Affairs within OMB on February 2, 2017, the administration indicates that the "two-for-one" provisions may apply not only to agency regulations, but also to significant agency guidance documents, and on September 8, 2017, the FDA published notices in the Federal Register soliciting broad public comment to identify regulations that could be modified in compliance with these Executive Orders. It is difficult to predict how these requirements will be implemented, and the extent to which they will impact the FDA's ability to exercise its regulatory authority. If these executive actions impose constraints on FDA's ability to engage in oversight and implementation activities in the normal course, our business may be negatively impacted.

Our relationships with healthcare providers, physicians and third-party payors will be subject to applicable anti-kickback, fraud and abuse, privacy and transparency and other healthcare laws and regulations, which could expose us to criminal sanctions, civil penalties, exclusion from government healthcare programs, contractual damages, reputational harm and diminished profits and future earnings.

Healthcare providers, physicians and third-party payors will play a primary role in the recommendation and prescription of any products for which we obtain regulatory approval. Our future arrangements with third party payors, healthcare providers and physicians may expose us to broadly applicable fraud and abuse and other healthcare laws and regulations, in addition to legal obligations related to privacy, data protection and information security, that may constrain the business or financial arrangements and relationships through which we conduct our operations, including how we research, market, sell and distribute any products for which we obtain regulatory approval. These include the following:

- **Anti-Kickback Statute**—The federal healthcare anti-kickback statute 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, order or recommendation or arranging of, any good or service, for which payment may be made under a federal healthcare program such as Medicare and Medicaid. A person or entity can be found guilty of violating the federal Anti-Kickback Statute without actual knowledge of the statute or specific intent to violate it in order to have committed a violation. In addition, the government may assert that a claim including items or services resulting from a violation of the Anti-Kickback Statute constitutes a false or fraudulent claim for purposes of the federal False Claims Act or federal civil money penalties statute;

- **False Claims Act**—The federal False Claims Act imposes 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 false or fraudulent claims for payment by a federal healthcare program; making a false statement or record material to a false or fraudulent claim or an obligation to pay money to the federal government; or avoiding, decreasing or concealing an obligation to pay money to the federal government. A claim that includes items or services resulting from a violation of the Anti-Kickback Statute constitutes a false or fraudulent claim under the False Claims Act. Potential liability for violating the False Claims Act includes mandatory treble damages and significant per-claim penalties;

- **HIPAA**—The federal Health Insurance Portability and Accountability Act of 1996, or HIPAA, imposes criminal and civil liability for executing a scheme to defraud any healthcare benefit program or making false statements relating to healthcare matters. Similar to the Anti-Kickback Statute, a person or entity does not need to have actual knowledge of the statute or specific intent to violate it in order to have committed a violation. In addition, HIPAA and, as amended by the Health Information Technology for Economic and Clinical Health Act and its implementing regulations, also imposes obligations on covered entities and their business associates, including mandatory contractual terms and technical safeguards, with respect to maintaining the privacy, security and transmission of individually identifiable health information;

- **Transparency Requirements**—Federal laws require applicable manufacturers of covered drugs to report payments and other transfers of value to physicians, including doctors, dentists, optometrists, podiatrists and chiropractors, and teaching hospitals, as well as information regarding ownership and investment interests held by the physicians described above and their immediate family members; and

- **Analogous State and Foreign Laws**—Analogous state and foreign fraud and abuse laws and regulations, such as state anti-kickback and false claims laws, can apply to our business practices, including but not limited to research, distribution, sales or marketing arrangements and claims involving healthcare items or services reimbursed by non-governmental third party payors and are generally broad and are enforced by many different federal and state agencies as well as through private actions.

- **European Privacy Laws**—The data privacy regime in the EU imposes obligations and restrictions on the collection and use of personal data relating to individuals located in the EU and includes the GDPR, and any national laws implementing or supplementing the GDPR. If we do not comply with our obligations under the EU privacy regime, we could be exposed to significant fines and we may be the subject of litigation and/or adverse publicity, which could have material adverse effect on our reputation and business.

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 and require manufacturers to report information related to payments and other transfers of value to physicians and other healthcare providers or marketing expenditures and pricing information. 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 pre-empted by HIPAA, thus complicating compliance efforts.

Efforts to ensure that our business arrangements with third parties, and our business generally, will comply with applicable healthcare laws and regulations will involve substantial costs. It is possible that governmental authorities will conclude that our business practices may not comply with current or future statutes, regulations, agency guidance or case law involving applicable fraud and abuse or other healthcare laws and regulations. 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, damages, fines, imprisonment, exclusion from government funded healthcare programs, such as Medicare and Medicaid, and the curtailment or restructuring of our operations. Defending against any such actions can be costly, time-consuming and may require significant financial and personnel resources. Therefore, even if we are successful in defending against any such actions that may be brought against us, our business may be impaired. If any of the physicians or other healthcare providers or entities with whom we expect to do business is found to be not in compliance with applicable laws, they may be subject to criminal, civil or administrative sanctions, including exclusions from government funded healthcare programs.

The provision of benefits or advantages to physicians to induce or encourage the prescription, recommendation, endorsement, purchase, supply, order or use of medicinal products is generally not permitted in the countries that form part of the European Union. Some European Union Member States, like the United Kingdom, through the United Kingdom Bribery Act 2010, have enacted laws explicitly prohibiting the provision of these type of benefits and advantages. Infringements of these laws can result in substantial fines and imprisonment.

Payments made to physicians in certain European Union Member States (e.g., France or Belgium) must be publicly disclosed. Moreover, agreements with physicians often must be the subject of prior notification and approval by the physician's employer, his or her competent professional organization and/or the regulatory authorities of the individual European Union Member States. These requirements are provided in the European Union Member State national laws, industry codes (e.g. the European Federation of Pharmaceutical Industries and Associations Disclosure and Healthcare Professionals Codes) or professional codes of conduct. Failure to comply with these requirements could result in reputational risk, public reprimands, administrative penalties, fines or imprisonment.

We are subject to governmental regulation and other legal obligations, particularly related to privacy, data protection and information security, and we are subject to consumer protection laws that regulate our marketing practices and prohibit unfair or deceptive acts or practices. Our actual or perceived failure to comply with such obligations could harm our business.

The GDPR imposes strict requirements on controllers and processors of personal data, including special protections for "special category data," which includes health, biometric and genetic information of data subjects located in the EU. Further, GDPR provides a broad right for EU Member States to create supplemental national laws, such as laws relating to the processing of health, genetic and biometric data, which could further limit our ability to use and share such data or could cause our costs to increase, and harm our business and financial condition. GDPR grants individuals the opportunity to object to the processing of their personal information, allows them to request deletion of personal information in certain circumstances, and provides the individual with an express right to seek legal remedies in the event the individual believes his or her rights have been violated. Further, the GDPR imposes strict rules on the transfer of personal data out of the European Union to the United States or other regions that have not been deemed to offer "adequate" privacy protections.

Failure to comply with the requirements of the GDPR and the related national data protection laws of the European Union Member States, which may deviate slightly from the GDPR, may result in fines of up to 4% of global revenues, or €20,000,000, whichever is greater, and in addition to such fines, we may be the subject of litigation and/or adverse publicity, which could have material adverse effect on our reputation and business. As a result of the implementation of the GDPR, we are required to put in place additional mechanisms to ensure compliance with the new data protection rules. For example, the GDPR requires us to make more detailed disclosures to data subjects, requires disclosure of the legal basis on which we can process personal data, may make it harder for us to obtain valid consent for processing, will require the appointment of a data protection officer where sensitive personal data (i.e., health data) is processed on a large scale, introduces mandatory data breach notification requirements throughout the EU, imposes additional obligations on us when we are contracting with service providers and requires us to adopt appropriate privacy governance including policies, procedures, training and data audit.

We are subject to the supervision of local data protection authorities in those jurisdictions where we monitor the behavior of individuals in the EU (i.e., undertaking clinical trials).

We are also subject to evolving European privacy laws on electronic marketing and cookies. The EU is in the process of replacing the e-Privacy Directive (2002/58/EC) with a new set of rules taking the form of a regulation, which will be directly implemented in the laws of each European member state, without the need for further enactment. The draft ePrivacy Regulation imposes strict opt-in marketing rules with limited exceptions for business-to-business communications, alters rules on third-party cookies, web beacons and similar technology and significantly increases potential fines to the same levels as GDPR (i.e., the greater of 20,000,000 Euros or 4% of total global annual revenue). While the e-Privacy Regulation was originally intended to be adopted on May 25, 2018 (alongside the GDPR), it is still going through the European legislative process and commentators now expect it to be adopted during the middle or second half of 2020.

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

In the United States and foreign jurisdictions, there have been a number of legislative and regulatory changes and proposed changes regarding the healthcare system that could prevent or delay regulatory 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 regulatory approval. We expect that current laws, as well as other healthcare reform measures that may be adopted in the future, may result in additional reductions in Medicare and other healthcare funding, more rigorous coverage criteria, new payment methodologies and in additional downward pressure on the price that we, or any collaborators, may receive for any approved products.

In March 2010, President Obama signed into law the Patient Protection and Affordable Care Act, as amended by the Health Care and Education Reconciliation Act, or collectively the Affordable Care Act. Among the provisions of the Affordable Care Act of potential importance to our business and our product candidates are the following:

- an annual, non-deductible fee on any entity that manufactures or imports specified branded prescription products and biologic products;
- an increase in the statutory minimum rebates a manufacturer must pay under the Medicaid Drug Rebate Program;
- a new methodology by which rebates owed by manufacturers under the Medicaid Drug Rebate Program are calculated for products that are inhaled, infused, instilled, implanted or injected;
- expansion of healthcare fraud and abuse laws, including the civil False Claims Act and the federal Anti-Kickback Statute, new government investigative powers and enhanced penalties for noncompliance;
- a new Medicare Part D coverage gap discount program, in which manufacturers must agree to offer 50% point-of-sale discounts off negotiated prices of applicable brand products to eligible beneficiaries during their coverage gap period, as a condition for the manufacturer’s outpatient products to be covered under Medicare Part D;
- extension of manufacturers’ Medicaid rebate liability to individuals enrolled in Medicaid managed care organizations;
- expansion of eligibility criteria for Medicaid programs;
- expansion of the entities eligible for discounts under the Public Health Service pharmaceutical pricing program;
- new requirements to report certain financial arrangements with physicians and teaching hospitals;

- a new requirement to annually report product samples that manufacturers and distributors provide to physicians;
- a new Patient-Centered Outcomes Research Institute to oversee, identify priorities in, and conduct comparative clinical effectiveness research, along with funding for such research; and
- established the Center for Medicare and Medicaid Innovation within CMS to test innovative payment and service delivery models.

Members of the United States Congress and the Trump Administration have expressed an intent to pass legislation or adopt executive orders to fundamentally change or repeal parts of the Affordable Care Act. At the executive branch level, on January 20, 2017, President Trump signed an Executive Order directing federal agencies with authorities and responsibilities under the Affordable Care Act to waive, defer, grant exemptions from, or delay the implementation of any provision of the Affordable Care Act that would impose a fiscal burden on states or a cost, fee, tax, penalty or regulatory burden on individuals, healthcare providers, health insurers, or manufacturers of pharmaceuticals or medical devices.

On October 13, 2017, President Trump signed an Executive Order terminating the cost-sharing subsidies that reimburse insurers under the Affordable Care Act. Several state Attorneys General filed suit to stop the administration from terminating the subsidies, but their request for a restraining order was denied by a federal judge in California on October 25, 2017. Further, on June 14, 2018, the U.S. Court of Appeals for the Federal Circuit ruled that the federal government was not required to pay more than $12 billion in Affordable Care Act risk corridor payments to third-party payors. The effects of this gap in reimbursement on third-party payors, the viability of the Affordable Care Act marketplace, providers, and our business, are not yet known. In addition, CMS has recently proposed regulations that would give states greater flexibility in setting benchmarks for insurers in the individual and small group marketplaces, which may have the effect of relaxing the essential health benefits required under the Affordable Care Act for plans sold through such marketplaces.

While Congress has not passed repeal legislation to date, the 2017 Tax Reform Act includes a provision repealing the individual insurance coverage mandate included in the Affordable Care Act, effective January 1, 2019. On December 14, 2018, a U.S. District Court Judge in Texas ruled that the Affordable Care Act is unconstitutional in its entirety because the “individual mandate” was repealed by Congress as part of the Tax Cuts and Jobs Act. While such U.S. District Court Judge, as well as the Trump Administration and CMS, have stated that the ruling will have no immediate effect pending appeal of the decision, it is unclear how this decision, subsequent appeals, and other efforts to repeal and replace the Affordable Care Act will impact the Affordable Care Act and our business.

In addition, other legislative changes have been proposed and adopted since the Affordable Care Act was enacted. In August 2011, the Budget Control Act of 2011, among other things, included aggregate reductions to Medicare payments to providers of 2% per fiscal year, which went into effect in April 2013 and will remain in effect through 2027 unless additional Congressional action is taken. The American Taxpayer Relief Act of 2012, among other things, reduced Medicare payments to several providers and increased the statute of limitations period for the government to recover overpayments to providers from three to five years. These new laws may result in additional reductions in Medicare and other healthcare funding and otherwise affect the prices we may obtain for any of our product candidates for which we may obtain regulatory approval or the frequency with which any such product candidate is prescribed or used.

The costs of prescription pharmaceuticals in the United States has also been the subject of considerable discussion in the United States, and members of Congress and the Trump Administration have stated that they will address such costs through new legislative and administrative measures. There have been several U.S. Congressional inquiries and proposed and enacted state legislation designed to, among other things, bring more transparency to drug pricing, review the relationship between pricing and manufacturer patient programs, reduce the costs of drugs under Medicare and reform government program reimbursement methodologies for drug products. At the federal level, Congress and the Trump administration have each indicated that it will continue to pursue new legislative and/or administrative measures to control drug costs. The Trump administration recently released a plan, or Blueprint, to reduce the cost of drugs. The Trump administrations’ Blueprint contains certain measures that the U.S. Department of Health and Human Services is already working to implement. Further, on January 31, 2019, the Department of Health and Human Services’ Office of Inspector General proposed modifications to U.S. federal Anti-Kickback Statute safe harbors which, among other things, will affect rebates paid by manufacturers to Medicare Part D plan sponsors, Medicaid managed care organizations, and those entities’ pharmacy benefit managers (“PBMs”), the purpose of which is to further reduce the cost of drug products to consumers.

Individual state legislatures have become increasingly aggressive in passing legislation and implementing regulations designed to control pharmaceutical and biological product pricing. Some of these measures include price or patient reimbursement constraints, discounts, restrictions on certain product access, marketing cost disclosure and transparency measures, and, in some cases, measures designed to encourage importation from other countries and bulk purchasing. In addition, regional health care authorities and individual hospitals are increasingly using bidding procedures to determine what pharmaceutical products and which suppliers will be included in their prescription drug and other health care programs. These measures could reduce the ultimate demand for our products, once approved, or put pressure on our product pricing.

In addition, individual states in the United States have also become increasingly active in passing legislation and implementing regulations designed to control pharmaceutical product pricing, including price or patient reimbursement constraints, discounts, restrictions on certain product access, and to encourage importation from other countries and bulk purchasing.

The pricing of prescription pharmaceuticals is also subject to governmental control outside the United States. In these countries, pricing negotiations with governmental authorities can take considerable time after the receipt of regulatory approval for a product. To obtain reimbursement or pricing approval in some countries, we may be required to conduct a clinical trial that compares the cost-effectiveness of our product candidates to other available therapies. If reimbursement of our products is unavailable or limited in scope or amount, or if pricing is set at unsatisfactory levels, our ability to generate revenues and become profitable could be impaired.

Governments outside the United States may impose strict price controls, which may adversely affect our revenues, if any.

In some countries, including Member States of the European Union, the pricing of prescription drugs is subject to governmental control. Additional countries may adopt similar approaches to the pricing of prescription drugs. In such countries, pricing negotiations with governmental authorities can take considerable time after receipt of regulatory approval for a product. In addition, there can be considerable pressure by governments and other stakeholders on prices and reimbursement levels, including as part of cost containment measures. Political, economic and regulatory developments may further complicate pricing negotiations, and pricing negotiations may continue after coverage and reimbursement have been obtained. Reference pricing used by various countries and parallel distribution, or arbitrage between low-priced and high-priced countries, can further reduce prices. In some countries, we may be required to conduct a clinical study or other studies that compare the cost-effectiveness of any of our product candidates to other available therapies in order to obtain or maintain reimbursement or pricing approval, which is time-consuming and costly. We cannot be sure that such prices and reimbursement will be acceptable to us or our strategic partners. Publication of discounts by third-party payors or authorities may lead to further pressure on the prices or reimbursement levels within the country of publication and other countries. If pricing is set at unsatisfactory levels or if reimbursement of our products is unavailable or limited in scope or amount, our revenues from sales by us or our strategic partners and the potential profitability of any of our product candidates in those countries would be negatively affected.

Laws and regulations governing any international operations we may have in the future may preclude us from developing, manufacturing and selling certain products outside of the United States and require us to develop and implement costly compliance programs.

If we further expand our operations outside of the United States, we must dedicate additional resources to comply with numerous laws and regulations in each jurisdiction in which we plan to operate. The Foreign Corrupt Practices Act, or FCPA, prohibits any U.S. individual or business from paying, offering, authorizing payment or offering of anything of value, directly or indirectly, to any foreign official, political party or candidate for the purpose of influencing any act or decision of the foreign entity in order to assist the individual or business in obtaining or retaining business. The FCPA also obligates companies whose securities are listed in the United States to comply with certain accounting provisions requiring us to maintain books and records that accurately and fairly reflect all transactions of the corporation, including international subsidiaries, and to devise and maintain an adequate system of internal accounting controls for international operations.

Compliance with the FCPA is expensive and difficult, particularly in countries in which corruption is a recognized problem. In addition, the FCPA presents particular 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 FCPA enforcement actions.

Various laws, regulations and executive orders also restrict the use and dissemination outside of the United States, or the sharing with certain non-U.S. nationals, of information classified for national security purposes, as well as certain products and technical data relating to those products. If we expand our presence outside of the United States, it will require us to dedicate additional resources to comply with these laws, and these laws may preclude us from developing, manufacturing, or selling certain products and product candidates outside of the United States, which could limit our growth potential and increase our development costs.

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. The Securities and Exchange Commission, or SEC, also may suspend or bar issuers from trading securities on U.S. exchanges for violations of the FCPA's accounting provisions.

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

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

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

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

Risks Related to Our Intellectual Property

Our commercial success depends on our ability to protect our intellectual property and proprietary technology.

Our commercial success depends in large part on our ability to obtain and maintain intellectual property rights protection through patents, trademarks, and trade secrets in the United States and other countries with respect to our proprietary product candidates. If we do not adequately protect our intellectual property rights, competitors may be able to erode, negate or preempt any competitive advantage we may have, which could harm our business and ability to achieve profitability. To protect our proprietary position, we have patent applications and may file other patent applications in the United States or abroad related to our product candidates that are important to our business; we may also license or purchase patent applications filed by others. The patent application and approval process is expensive and time-consuming. We may not be able to file and prosecute all necessary or desirable patent applications at a reasonable cost or in a timely manner.

Agreements through which we license patent rights may not give us control over patent prosecution or maintenance, so that we may not be able to control which claims or arguments are presented, how claims are amended, and may not be able to secure, maintain, or successfully enforce necessary or desirable patent protection from those patent rights. We have not had and do not have primary control over patent prosecution and maintenance for certain of the patents and patent applications we license, and therefore cannot guarantee that these patents and applications will be prosecuted or maintained in a manner consistent with the best interests of our business. We cannot be certain that patent prosecution and maintenance activities by our licensors have been or will be conducted in compliance with applicable laws and regulations or will result in valid and enforceable patents.

If the scope of the patent protection we or our licensors obtain is not sufficiently broad, we may not be able to prevent others from developing and commercializing technology and products similar or identical to ours. The degree of patent protection we require to successfully compete in the marketplace may be unavailable or severely limited in some cases

and may not adequately protect our rights or permit us to gain or keep any competitive advantage. We cannot provide any assurances that any of our licensed patents have, or that any of our pending owned or licensed patent applications that mature into issued patents will include, claims with a scope sufficient to protect our proprietary platform or otherwise provide any competitive advantage, nor can we assure you that our licenses are or will remain in force. Other parties have developed or may develop technologies that may be related or competitive with our approach, and may have filed or may file patent applications and may have been issued or may be issued patents with claims that overlap or conflict with our patent applications, either by claiming the same compounds, formulations or methods or by claiming subject matter that could dominate our patent position. In addition, the laws of foreign countries may not protect our rights to the same extent as the laws of the United States. Furthermore, patents have a limited lifespan. In the United States, the natural expiration of a patent is generally twenty years after it is filed. Various extensions may be available; however, the life of a patent, and the protection it affords, is limited. 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. As a result, our patent portfolio may not provide us with adequate and continuing patent protection sufficient to exclude others from commercializing products similar to our product candidates. In addition, the patent portfolio licensed to us is, or may be, licensed to third parties, such as outside our field, and such third parties may have certain enforcement rights. Thus, patents licensed to us could be put at risk of being invalidated or interpreted narrowly in litigation filed by or against another licensee or in administrative proceedings brought by or against another licensee in response to such litigation or for other reasons.

Even if they are unchallenged, our owned and licensed patents and pending patent applications, if issued, may not provide us with any meaningful protection or prevent competitors from designing around our patent claims to circumvent our patents by developing similar or alternative technologies or therapeutics in a non-infringing manner. For example, a third party may develop a competitive therapy that provides benefits similar to one or more of our product candidates but falls outside the scope of our patent protection or license rights. If the patent protection provided by the patents and patent applications we hold or pursue with respect to our product candidates is not sufficiently broad to impede such competition, our ability to successfully commercialize our product candidates could be negatively affected, which would harm our business. Currently, a significant portion of our patents and patent applications are in-licensed, though similar risks would apply to any patents or patent applications that we now own or may own or in-license in the future.

We, or any future partners, collaborators, or licensees, may fail to identify patentable aspects of inventions made in the course of development and commercialization activities before it is too late to obtain patent protection on them. Therefore, we may miss potential opportunities to strengthen our patent position.

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, for example with respect to proper priority claims, inventorship, claim scope, or requests for patent term adjustments. If we or our partners, collaborators, licensees, or licensors, whether current or future, fail to establish, maintain or protect such patents and other intellectual property rights, such rights may be reduced or eliminated. If our partners, collaborators, licensees, or licensors, 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. If there are material defects in the form, preparation, prosecution, or enforcement of our patents or patent applications, such patents may be invalid and/or unenforceable, and such applications may never result in valid, enforceable patents. Any of these outcomes could impair our ability to prevent competition from third parties, which may have an adverse impact on our business.

The patent position of biotechnology and pharmaceutical companies carries uncertainty. In addition, the determination of patent rights with respect to pharmaceutical compounds commonly involves complex legal and factual questions, which are dependent upon the current legal and intellectual property context, extant legal precedent and interpretations of the law by individuals. As a result, the issuance, scope, validity, enforceability and commercial value of our patent rights are characterized by uncertainty.

Pending patent applications cannot be enforced against third parties practicing the technology claimed in such applications unless and until a patent issues from such applications. Assuming the other requirements for patentability are met, currently, the first to file a patent application is generally entitled to the patent. However, prior to March 16, 2013, in the United States, the first to invent was entitled to the patent. Publications of discoveries in the scientific literature often lag behind the actual discoveries, and patent applications in the United States and other jurisdictions are 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, we cannot be certain that parties from whom we do or may license or purchase patent rights were the first to make relevant claimed inventions, or were the first to file for patent protection for them. If third parties have filed

prior patent applications on inventions claimed in our patents or applications that were filed on or before March 15, 2013, an interference proceeding in the United States can be initiated by such third parties to determine who was the first to invent any of the subject matter covered by the patent claims of our applications. If third parties have filed such prior applications after March 15, 2013, a derivation proceeding in the United States can be initiated by such third parties to determine whether our invention was derived from theirs.

Moreover, because the issuance of a patent is not conclusive as to its inventorship, scope, validity or enforceability, our patents or pending patent applications may be challenged in the courts or patent offices in the United States and abroad. There is no assurance that all of the potentially relevant prior art relating to our patents and patent applications has been found. If such prior art exists, it may be used to invalidate a patent, or may prevent a patent from issuing from a pending patent application. For example, such patent filings may be subject to a third-party submission of prior art to the U.S. Patent and Trademark Office, or USPTO, or to other patent offices around the world. Alternately or additionally, we may become involved in post-grant review procedures, oppositions, derivation proceedings, *ex parte* reexaminations, *inter partes* review, supplemental examinations, or interference proceedings or challenges in district court, in the United States or in various foreign patent offices, including both national and regional, challenging patents or patent applications in which we have rights, including patents on which we rely to protect our business. An adverse determination in any such challenges may result in loss of the patent or in patent or patent application claims being narrowed, invalidated or held unenforceable, in whole or in part, or in denial of the patent application or loss or reduction in the scope of one or more claims of the patent or patent application, any of 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. 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.

Pending and future patent applications may not result in patents being issued that protect our business, in whole or in part, or which effectively prevent others from commercializing competitive products. Competitors may also be able to design around our patents. 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 or in the same manner as the laws of the United States. For example, patent laws in various jurisdictions, including significant commercial markets such as Europe, restrict the patentability of methods of treatment of the human body more than United States law does. If these developments were to occur, they could have a material adverse effect on our ability to generate revenue.

The patent application process is subject to numerous risks and uncertainties, and there can be no assurance that we or any of our future development partners will be successful in protecting our product candidates by obtaining and defending patents. These risks and uncertainties include the following:

- the USPTO and various foreign governmental patent agencies require compliance with a number of procedural, documentary, fee payment and other provisions during the patent process. There are situations in which noncompliance can result in abandonment or lapse of a patent or patent application, resulting in partial or complete loss of patent rights in the relevant jurisdiction. In such an event, competitors might be able to enter the market earlier than would otherwise have been the case;

- patent applications may not result in any patents being issued;

- patents that may be issued or in-licensed may be challenged, invalidated, modified, revoked, circumvented, found to be unenforceable or otherwise may not provide any competitive advantage;

- our competitors, many of whom have substantially greater resources and many of whom have made significant investments in competing technologies, may seek or may have already obtained patents that will limit, interfere with or eliminate our ability to make, use, and sell our potential product candidates;

- there may be significant pressure on the U.S. government and international governmental bodies to limit the scope of patent protection both inside and outside the United States for disease treatments that prove successful, as a matter of public policy regarding worldwide health concerns; and

- countries other than the United States may have patent laws less favorable to patentees than those upheld by U.S. courts, allowing foreign competitors a better opportunity to create, develop and market competing product candidates.

Issued patents that we have or may obtain or license may not provide us with any meaningful protection, prevent competitors from competing with us or otherwise provide us with any competitive advantage. Our competitors may be able to circumvent our patents by developing similar or alternative technologies or products in a non-infringing manner. Our competitors may also seek approval to market their own products similar to or otherwise competitive with our products. Alternatively, our competitors may seek to market generic versions of any approved products by submitting ANDAs to the FDA in which they claim that patents owned or licensed by us are invalid, unenforceable or not infringed. In these circumstances, we may need to defend or assert our patents, or both, 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 or unenforceable, or that our competitors are competing in a non-infringing manner. Thus, even if we have valid and enforceable patents, these patents still may not provide protection against competing products or processes sufficient to achieve our business objectives.

In addition, we rely on the protection of our trade secrets and proprietary, unpatented know-how. Although we have taken steps to protect our trade secrets and unpatented know-how, including entering into confidentiality agreements with third parties, and confidential information and invention assignment agreements with employees, consultants, collaborators, vendors, and advisors, we cannot provide any assurances that all such agreements have been duly executed, and third parties may still obtain this information or may come upon this or similar information independently. It is possible that technology relevant to our business will be independently developed by a person who is not a party to such a confidentiality or invention assignment agreement. We may not be able to prevent the unauthorized disclosure or use of our technical knowledge or trade secrets by consultants, collaborators, vendors, advisors, former employees and current employees. Furthermore, if the parties to our confidentiality agreements breach or violate the terms of these agreement, we may not have adequate remedies for any such breach or violation, and we could lose our trade secrets as a consequence of such breaches or violations. Our trade secrets could otherwise become known or be independently discovered by our competitors. Additionally, if the steps taken to maintain our trade secrets are deemed inadequate, we may have insufficient recourse against third parties for misappropriating our trade secrets. If any of these events occurs or if we otherwise lose protection for our trade secrets or proprietary know-how, our business may be harmed.

We depend on intellectual property licensed from third parties and termination of any of these licenses could result in the loss of significant rights, which would harm our business.

In March 2017, we entered into a license agreement with Novartis, or the Novartis License, pursuant to which we were granted an exclusive, field-restricted, worldwide license to certain intellectual property rights owned or controlled by Novartis, including patents, patent applications, proprietary information, know-how and other intellectual property, to develop, commercialize and sell one or more therapeutic products comprising RTB101 or RTB101 and everolimus in a fixed dose combination.

We are dependent on these patents, know-how and proprietary technology, licensed from Novartis. Any termination of this license, or a finding that such intellectual property lacks legal effect, could result in the loss of significant rights and could harm our ability to commercialize any product candidates. See the section entitled “Business—Intellectual Property” for additional information regarding our license agreements.

Disputes may also arise between us and our licensor, our licensor and its licensors, or us and third parties that co-own intellectual property with our licensor or its licensors, regarding intellectual property subject to a license agreement, including those relating to:

- the scope of rights, if any, granted under the license agreement and other interpretation-related issues;
- whether and the extent to which our technology and processes infringe on intellectual property of the licensor that is not subject to the license agreement;
- whether our licensor or its licensor had the right to grant the license agreement;
- whether third parties are entitled to compensation or equitable relief, such as an injunction, for our use of the intellectual property without their authorization;
- our right to sublicense patent and other rights to third parties under collaborative development relationships;
- whether we are complying with our obligations with respect to the use of the licensed technology in relation to our development and commercialization of product candidates;

- our involvement in the prosecution of the licensed patents and our licensors' overall patent enforcement strategy;
- the allocation of ownership of inventions and know-how resulting from the joint creation or use of intellectual property by our licensors and by us and our partners; and
- the amounts of royalties, milestones or other payments due under the license agreement.

If disputes over intellectual property that we have licensed prevent or impair our ability to maintain our current licensing arrangements on acceptable terms, or are insufficient to provide us the necessary rights to use the intellectual property, we may be unable to successfully develop and commercialize the affected product candidates. If we or any such licensors fail to adequately protect this intellectual property, our ability to commercialize our products could suffer.

Novartis may partially terminate the license agreement with respect to everolimus if we fail or cease for three years to use commercially reasonable efforts to research, develop and commercialize a product using everolimus, provided that our license related to RTB101 and Novartis's license to our improvements related to everolimus will continue. Additionally, either party may terminate the Novartis License if the other party commits a material breach and fails to cure such breach within 60 days after written notice. If Novartis unilaterally terminates the Novartis License, the research and development of RTB101 or RTB101 and everolimus in a fixed dose combination would be suspended, and we may be unable to research, develop and license future product candidates.

We may be required to pay certain milestones and royalties under our license agreements with third-party licensors.

Under our current and future license agreements, we may be required to pay milestones and royalties based on our revenues from sales of our products utilizing the technologies licensed or sublicensed from Novartis or other licensors and these royalty payments could adversely affect the overall profitability for us of any products that we may seek to commercialize. In order to maintain our license rights under current and future license agreements, we may need to meet certain specified milestones, subject to certain cure provisions, in the development of our product candidates and in the raising of funding. In addition, these agreements may contain diligence milestones and we may not be successful in meeting all of the milestones in the future on a timely basis or at all, which could result in termination of our rights under such agreements. We may need to outsource and rely on third parties for many aspects of the clinical development, sales and marketing of our products covered under our current and future license agreements. Delay or failure by these third parties could adversely affect the continuation of our license agreements with their third-party licensors.

It is difficult and costly to protect our intellectual property and our proprietary technologies, and we may not be able to ensure their protection.

Our commercial success will depend in part on obtaining and maintaining patent protection and trade secret protection for the use, formulation and structure of our products and product candidates, the methods used to manufacture them, the related therapeutic targets and associated methods of treatment as well as on successfully defending these patents against potential third-party challenges. Our ability to protect our products and product candidates from unauthorized making, using, selling, offering to sell or importing by third parties is dependent on the extent to which we have rights under valid and enforceable patents that cover these activities.

The patent positions of pharmaceutical, biotechnology and other life sciences companies can be highly uncertain and involve complex legal and factual questions for which important legal principles remain unresolved. Changes in either the patent laws or in interpretations of patent laws in the United States and other countries may diminish the value of our intellectual property. Further, the determination that a patent application or patent claim meets all of the requirements for patentability is a subjective determination based on the application of law and jurisprudence. The ultimate determination by the USPTO or by a court or other trier of fact in the United States, or corresponding foreign national patent offices or courts, on whether a claim meets all requirements of patentability cannot be assured. Although we have conducted searches for third-party publications, patents and other information that may affect the patentability of claims in our various patent applications and patents, we cannot be certain that all relevant information has been identified. Accordingly, we cannot predict the breadth of claims that may be allowed or enforced in our owned patents or patent applications, in our licensed patents or patent applications or in third-party patents.

We cannot provide assurances that any of our patent applications will be found to be patentable, including over our own or our licensors' prior art publications or patent literature, or will issue as patents. Neither can we make assurances as to

the scope of any claims that may issue from our pending and future patent applications nor to the outcome of any proceedings by any potential third parties that could challenge the patentability, validity or enforceability of our patents and patent applications in the United States or foreign jurisdictions. Any such challenge, if successful, could limit patent protection for our products and product candidates and/or materially harm our business.

The degree of future protection for our proprietary rights is uncertain because legal means afford only limited protection and may not adequately protect our rights or permit us to gain or keep our competitive advantage. For example:

- we may not be able to generate sufficient data to support full patent applications that protect the entire breadth of developments in one or more of our programs;
- it is possible that one or more of our pending patent applications will not become an issued patent or, if issued, that the patent(s) claims will have sufficient scope to protect our technology, provide us with a basis for commercially viable products or provide us with any competitive advantages;
- if our pending applications issue as patents, they may be challenged by third parties as not infringed, invalid or unenforceable under United States or foreign laws;
- if issued, the patents under which we hold rights may not be valid or enforceable;
- we may not successfully commercialize RTB101, alone or in combination with a rapalog, such as everolimus or sirolimus, if approved, before our relevant patents expire;
- we may not be the first to make the inventions covered by each of our patents and pending patent applications; or
- we may not develop additional proprietary technologies or product candidates that are separately patentable.

In addition, to the extent that we are unable to obtain and maintain patent protection for one of our products or product candidates or in the event that such patent protection expires, it may no longer be cost-effective to extend our portfolio by pursuing additional development of a product or product candidate for follow-on indications.

We also may rely on trade secrets to protect our technologies or products, especially where we do not believe patent protection is appropriate or obtainable. Also, we cannot provide any assurances that any of our licensed patents have claims with a scope sufficient to protect our technology or otherwise provide any competitive advantage, nor can we assure you that our licenses are or will remain in full force or effect, in which case we would similarly rely on trade secrets. However, trade secrets are difficult to protect. Although we use reasonable efforts to protect our trade secrets, our employees, consultants, contractors, outside scientific collaborators and other advisers may unintentionally or willfully disclose our information to competitors. Enforcing a claim that a third-party entity illegally obtained and is using any of our trade secrets is expensive and time-consuming, and the outcome is unpredictable. In addition, courts outside the United States are sometimes less willing to protect trade secrets. Moreover, our competitors may independently develop equivalent knowledge, methods and know-how. Notably, proprietary technology protected by a trade secret does not preempt the patenting of independently developed equivalent technology, even if such equivalent technology is invented subsequent to the technology protected by a trade secret.

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

Periodic maintenance fees, renewal fees, annuity fees and various other governmental fees on patents and applications are required to be paid to the USPTO and various governmental patent agencies outside of the United States in several stages over the lifetime of the patents and applications. The USPTO and various non-U.S. governmental patent agencies require compliance with a number of procedural, documentary, fee payment and other similar provisions during the patent application process and after a patent has issued. There are situations in which non-compliance can result in abandonment or lapse of the patent or patent application, resulting in partial or complete loss of patent rights in the relevant jurisdiction. In such a circumstance, competitors may be able to enter the market earlier than otherwise would be the case. Under the terms of some of our current and future licenses, we may not have the ability to maintain patents or prosecute patent applications in the portfolio and may therefore have to rely on third parties to comply with these requirements.

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

Given the amount of time required for the development, testing and regulatory review of new product candidates, patents protecting such candidates might expire before or shortly after such candidates are commercialized. We expect to seek extensions of patent terms in the United States and, if available, in other countries where we are prosecuting patents. In the United States, the Drug Price Competition and Patent Term Restoration Act of 1984 permits a patent term extension of up to five years beyond the normal expiration of the patent, which is limited to the approved indication (or any additional indications approved during the period of extension). We might not be granted an extension because of, for example, failure to apply within applicable periods, failure to apply prior to the expiration of relevant patents or otherwise failure to satisfy any of the numerous applicable requirements. Moreover, the applicable authorities, including the FDA and the USPTO in the United States, and any equivalent regulatory authority in other countries, may not agree with our assessment of whether such extensions are available, and may refuse to grant extensions to our patents, or may grant more limited extensions than we request. If this occurs, our competitors may be able to obtain approval of competing products following our patent expiration by referencing our clinical and preclinical data and launch their product earlier than might otherwise be the case. If this were to occur, it could have a material adverse effect on our ability to generate revenue.

Changes to patent law in the United States and other jurisdictions could diminish the value of patents in general, thereby impairing our ability to protect our products.

As is the case with other biopharmaceutical companies, our commercial success is heavily dependent on intellectual property, particularly patents. Obtaining and enforcing patents in the biopharmaceutical industry involves both technological and legal complexity and is therefore costly, time consuming and inherently uncertain. Recent wide-ranging patent reform legislation in the United States, including the Leahy-Smith America Invents Act, or the America Invents Act, could increase those uncertainties and costs. The America Invents Act was signed into law on September 16, 2011, and many of the substantive changes became effective on March 16, 2013. The America Invents Act reforms United States patent law in part by changing the U.S. patent system from a “first to invent” system to a “first inventor to file” system, expanding the definition of prior art, and developing a post-grant review system. This legislation changes United States patent law in a way that may weaken our ability to obtain patent protection in the United States for those applications filed after March 16, 2013.

Further, the America Invents Act created new procedures to challenge the validity of issued patents in the United States, including post-grant review and *inter partes* review proceedings, which some third parties have been using to cause the cancellation of selected or all claims of issued patents of competitors. For a patent with an effective filing date of March 16, 2013 or later, a petition for post-grant review can be filed by a third party in a nine-month window from issuance of the patent. A petition for *inter partes* review can be filed immediately following the issuance of a patent if the patent has an effective filing date prior to March 16, 2013. A petition for *inter partes* review can be filed after the nine-month period for filing a post-grant review petition has expired for a patent with an effective filing date of March 16, 2013 or later. Post-grant review proceedings can be brought on any ground of invalidity, whereas *inter partes* review proceedings can only raise an invalidity challenge based on published prior art and patents. These adversarial actions at the USPTO review patent claims without the presumption of validity afforded to U.S. patents in lawsuits in U.S. federal courts and use a lower burden of proof than used in litigation in U.S. federal courts. Therefore, it is generally considered easier for a competitor or third party to have a U.S. patent invalidated in a USPTO post-grant review or *inter partes* review proceeding than invalidated in a litigation in a U.S. federal court. If any of our patents are challenged by a third party in such a USPTO proceeding, there is no guarantee that we or our licensors or collaborators will be successful in defending the patent, which may result in a loss of the challenged patent right to us.

In addition, recent court rulings in cases such as *Association for Molecular Pathology v. Myriad Genetics, Inc., BRCA1- & BRCA2-Based Hereditary Cancer Test Patent Litigation, and Promega Corp. v. Life Technologies Corp.* have narrowed the scope of patent protection available in certain circumstances and weakened the rights of patent owners in certain situations. In addition to increasing uncertainty with regard to our ability to obtain patents in the future, this combination of events has created uncertainty with respect to the value of patents once obtained. Depending on future actions by the U.S. Congress, the U.S. courts, the USPTO and the relevant law-making bodies in other countries, the laws and regulations governing patents could change in unpredictable ways that would weaken our ability to obtain new patents or to enforce our existing patents and patents that we might obtain in the future.

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

Filing, prosecuting, enforcing and defending patents on our product candidates in all countries throughout the world would be prohibitively expensive, and our intellectual property rights in some countries outside the United States can be less extensive than those in the United States. The requirements for patentability may differ in certain countries, particularly in developing countries; thus, even in countries where we do pursue patent protection, there can be no assurance that any patents will issue with claims that cover our products.

Moreover, our ability to protect and enforce our intellectual property rights may be adversely affected by unforeseen changes in foreign intellectual property laws. Additionally, laws of some countries outside of the United States and Europe do not afford intellectual property protection to the same extent as the laws of the United States and Europe. Many companies have encountered significant problems in protecting and defending intellectual property rights in certain foreign jurisdictions. The legal systems of some countries, including India, China and other developing countries, do not favor the enforcement of patents and other intellectual property rights. This could make it difficult for us to stop the infringement of our patents or the misappropriation of our other intellectual property rights. For example, many foreign countries have compulsory licensing laws under which a patent owner must grant licenses to third parties. Consequently, we may not be able to prevent third parties from practicing our inventions in certain countries outside the United States and Europe or from selling or importing products made from our inventions in and into the United States or other jurisdictions. Competitors may use our technologies in jurisdictions where we have not obtained patent protection to develop and market their own products and, further, may export otherwise infringing products to territories where we have patent protection, if our ability to enforce our patents to stop infringing activities is inadequate. These products may compete with our products, and our patents or other intellectual property rights may not be effective or sufficient to prevent them from competing.

Agreements through which we license patent rights may not give us sufficient rights to permit us to pursue enforcement of our licensed patents or defense of any claims asserting the invalidity of these patents (or control of such enforcement or defense) of such patent rights in all relevant jurisdictions as requirements may vary.

Proceedings to enforce our patent rights, whether or not successful, could result in substantial costs and divert our efforts and resources from other aspects of our business. Moreover, such proceedings 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. Furthermore, while we intend to protect our intellectual property rights in major markets for our products, we cannot ensure that we will be able to initiate or maintain similar efforts in all jurisdictions in which we may wish to market our products, if approved. Accordingly, our efforts to protect our intellectual property rights in such countries may be inadequate.

Others may challenge inventorship or claim an ownership interest in our intellectual property which could expose it to litigation and have a significant adverse effect on its prospects.

A third party or former employee or collaborator may claim an ownership interest in one or more of our or our licensors' patents or other proprietary or intellectual property rights. A third party could bring legal actions against us and seek monetary damages and/or enjoin clinical testing, manufacturing and marketing of the affected product or products. While we are presently unaware of any claims or assertions by third-parties with respect to our patents or other intellectual property, we cannot guarantee that a third party will not assert a claim or an interest in any of such patents or intellectual property. If we become involved in any litigation, it could consume a substantial portion of our resources, and cause a significant diversion of effort by our technical and management personnel.

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

Our commercial success depends, in part, on our ability to develop, manufacture, market and sell our product candidates without infringing the intellectual property and other proprietary rights of third parties. Third parties may have U.S. and non-U.S. issued patents and pending patent applications relating to compounds, methods of manufacturing compounds and/or methods of use for the treatment of the disease indications for which we are developing our product candidates. If any third-party patents or patent applications are found to cover our product candidates or their methods of use or manufacture, we may not be free to manufacture or market our product candidates as planned without obtaining a license, which may not be available on commercially reasonable terms, or at all.

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 products candidates, including interference and post-grant proceedings before the USPTO. There may be third-party patents or patent applications with claims to materials, formulations, methods of manufacture or methods for treatment related to the composition, use or manufacture of our product candidates. We cannot guarantee that any of our patent searches or analyses including, but not limited to, the identification of relevant patents, the scope of patent claims or the expiration of relevant patents are complete or thorough, nor can we be certain that we have identified each and every patent and pending application in the United States and abroad that is relevant to or necessary for the commercialization of our product candidates in any jurisdiction. Because patent applications can take many years to issue, there may be currently pending patent applications which may later result in issued patents that our product candidates may be accused of infringing. In addition, third parties may obtain patents in the future and claim that use of our technologies infringes upon these patents. Accordingly, third parties may assert infringement claims against us based on intellectual property rights that exist now or arise in the future. The outcome of intellectual property litigation is subject to uncertainties that cannot be adequately quantified in advance. The pharmaceutical and biotechnology industries have produced a significant number of patents, and it may not always be clear to industry participants, including us, which patents cover various types of products or methods of use or manufacture. The scope of protection afforded by a patent is subject to interpretation by the courts, and the interpretation is not always uniform. If we were sued for patent infringement, we would need to demonstrate that our product candidates, products or methods either do not infringe the patent claims of the relevant patent or that the patent claims are invalid or unenforceable, and we may not be able to do this. Proving invalidity is difficult. For example, in the United States, proving invalidity requires a showing of clear and convincing evidence to overcome the presumption of validity enjoyed by issued patents. Even if we are successful in these proceedings, we may incur substantial costs and the time and attention of our management and scientific personnel could be diverted in pursuing these proceedings, which could significantly harm our business and operating results. In addition, we may not have sufficient resources to bring these actions to a successful conclusion.

If we are found to infringe a third party's intellectual property rights, 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 in order to use the infringing technology and continue developing, manufacturing or marketing the infringing product candidate or product. If we were required to obtain a license to continue to manufacture or market the affected product, we may be required to pay substantial royalties or grant cross-licenses to our patents. We cannot, however, assure you that any such license will be available on acceptable terms, if at all. Ultimately, we could be prevented from commercializing a product, or be forced to cease some aspect of our business operations as a result of claims of patent infringement or violation of other intellectual property rights, Further, the outcome of intellectual property litigation is subject to uncertainties that cannot be adequately quantified in advance, including the demeanor and credibility of witnesses and the identity of any adverse party. This is especially true in intellectual property cases that may turn on the testimony of experts as to technical facts upon which experts may reasonably disagree. Furthermore, 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; alternatively or additionally it could include terms that impede or destroy our ability to compete successfully in the commercial marketplace. In addition, we could be found liable for monetary damages, including treble damages and attorneys' fees if we are found to have willfully infringed a patent. A finding of infringement could prevent us from commercializing our product candidates or force us to cease some of our business operations, which could harm our business. Claims that we have misappropriated the confidential information or trade secrets of third parties could have a similar negative impact on our business.

We may be subject to claims by third parties asserting that our employees or we have misappropriated their intellectual property, or claiming ownership of what we regard as our own intellectual property.

Many of our current and former employees and our licensors' current and former employees, including our senior management, were previously employed at universities or at other biotechnology or pharmaceutical companies, including some which may be competitors or potential competitors. Some of these employees, including members of our senior management, may have executed proprietary rights, non-disclosure and non-competition agreements, or similar agreements, in connection with such previous employment. Although we try to ensure that our employees do not use the proprietary information or know-how of others in their work for us, we may be subject to claims that we or these employees have used or disclosed intellectual property, including trade secrets or other proprietary information, of any such third party. Litigation may be necessary to defend against such claims. If we fail in defending any such claims, in addition to paying monetary damages, we may sustain damages or lose key personnel, valuable intellectual property rights or the personnel's work product, which could hamper or prevent commercialization of our technology, which could materially affect our commercial development efforts. Such intellectual property rights could be awarded to a third party, and we could be required to obtain a license from such third party to commercialize our technology or products. Such a license may not be available on commercially reasonable terms or at all. Even if we are successful in defending against such claims, litigation could result in substantial costs and be a distraction to management.

In addition, while we typically require our employees, consultants and contractors who may be involved in the development of intellectual property to execute agreements assigning such intellectual property to us, we may be unsuccessful in executing such an agreement with each party who in fact develops intellectual property that we regard as our own, which may result in claims by or against us related to the ownership of such 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. Even if we are successful in prosecuting or defending against such claims, litigation could result in substantial costs and be a distraction to our senior management and scientific personnel.

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

Competitors may infringe our patents, trademarks, copyrights or other intellectual property. To counter infringement or unauthorized use, we may be required to file infringement claims, which can be expensive and time consuming and divert the time and attention of our management and scientific personnel. Any claims we assert against perceived infringers could provoke these parties to assert counterclaims against us alleging that we infringe their patents, in addition to counterclaims asserting that our patents are invalid or unenforceable, or both. In any patent infringement proceeding, there is a risk that a court will decide that a patent of ours is invalid or unenforceable, in whole or in part, and that we do not have the right to stop the other party from using the invention at issue. There is also a risk that, even if the validity of such patents is upheld, the court will construe the patent's claims narrowly or decide that we do not have the right to stop the other party from using the invention at issue on the grounds that our patent claims do not cover the invention. An adverse outcome in a litigation or proceeding involving one or more of our patents could limit our ability to assert those 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 trademarks in question. In this case, we could ultimately be forced to cease use of such trademarks.

Even if we establish infringement, the court may decide not to grant an injunction against further infringing activity and instead award only monetary damages, which may or may not be an adequate remedy. 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. There could also be public announcements of the results of hearings, motions or other interim proceedings or developments. If securities analysts or investors perceive these results to be negative, it could adversely affect the price of shares 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. Even if we ultimately prevail in such claims, the monetary cost of such litigation and the diversion of the attention of our management and scientific personnel could outweigh any benefit we receive as a result of the proceedings.

Additionally, for certain of our existing and future in-licensed patent rights, we may not have the right to bring suit for infringement and may have to rely on third parties to enforce these rights for us. If we cannot or choose not to take action against those we believe infringe our intellectual property rights, we may have difficulty competing in certain markets where such potential infringers conduct their business, and our commercialization efforts may suffer as a result.

If our trademarks and trade names are not adequately protected, then we may not be able to build name recognition in our trademarks of interest and our business may be adversely affected.

Our trademarks or trade names may be challenged, infringed, circumvented or declared generic or determined to be infringing on other marks. We rely on both registration and common law protection for our trademarks. We may not be able to protect our rights to these trademarks and trade names or may be forced to stop using these names, which we need for name recognition by potential partners or customers in our markets of interest. During trademark registration proceedings, we may receive rejections. Although we would be given an opportunity to respond to those rejections, we may be unable to overcome such rejections. In addition, in the USPTO and in comparable agencies in many foreign jurisdictions, third parties are given an opportunity to oppose pending trademark applications and to seek to cancel registered trademarks. Opposition or cancellation proceedings may be filed against our trademarks, and our trademarks may not survive such proceedings. Moreover, any name we propose to use for our products in the United States must be approved by the FDA, regardless of whether we have registered it, or applied to register it, as a trademark. The FDA typically conducts a review of proposed product names, including an evaluation of potential for confusion with other product names. If the FDA objects to any of our proposed product names, we may be required to expend significant additional resources in an effort to identify a usable substitute 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 establish name recognition based on our trademarks and trade names, we may not be able to compete effectively and our business may be adversely affected.

Risks Related to Our Dependence on Third Parties

We rely on third parties to assist in conducting our clinical trials. If they do not perform satisfactorily, we may not be able to obtain regulatory approval or commercialize our product candidates, or such approval or commercialization may be delayed, and our business could be substantially harmed.

We do not independently conduct clinical trials of any of our product candidates. We have relied upon and plan to continue to rely on third parties, such as contract research organizations, clinical data management organizations, medical institutions and clinical investigators, to conduct these clinical trials and expect to rely on these third parties to conduct clinical trials of any other product candidate that we develop. Any of these third parties may terminate their engagements with us under certain circumstances. We may not be able to enter into alternative arrangements or do so on commercially reasonable terms. In addition, there is a natural transition period when a new CRO begins work. As a result, delays may occur, which could negatively impact our ability to meet our expected clinical development timelines and harm our business, financial condition and prospects.

Further, although our reliance on these third parties for clinical development activities limits our control over these activities, we remain responsible for ensuring that each of our trials is conducted in accordance with the applicable protocol, legal and regulatory requirements and scientific standards. For example, notwithstanding the obligations of a CRO for a trial of one of our product candidates, we remain responsible for ensuring that each of our clinical trials is conducted in accordance with the general investigational plan and protocols for the trial. Moreover, the FDA requires us to comply with requirements, 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. The FDA enforces these GCPs through periodic inspections of trial sponsors, principal investigators, clinical trial sites and IRBs. If we or our third-party contractors fail to comply with applicable GCPs, the clinical data generated in our clinical trials may be deemed unreliable and the FDA may require us to perform additional clinical trials before approving our product candidates, which would delay the regulatory approval process. We cannot be certain that, upon inspection, the FDA will determine that any of our clinical trials comply with GCPs. We are also required to register certain clinical trials and post the results of completed clinical trials on a government-sponsored database, ClinicalTrials.gov, within certain timeframes. Failure to do so can result in fines, adverse publicity and civil and criminal sanctions.

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

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

Our use of third parties to manufacture our product candidates and products which we are studying in combination with our product candidates may increase the risk that we will not have sufficient quantities of our product candidates, products, or necessary quantities of such materials on time or at an acceptable cost.

We do not own or operate manufacturing facilities for the production of clinical or commercial quantities of our product candidates, and we lack the resources and the capabilities to do so. As a result, we currently rely on third parties for the manufacture and supply of the active pharmaceutical ingredients, or API, in our product candidates. Our current strategy is to outsource all manufacturing of our product candidates to third parties.

We currently engage one third-party manufacturer to provide the active pharmaceutical ingredient, or API, and two other third-party manufacturers to provide services for the final drug product formulation of RTB101 that is being used in our clinical trials. Although we believe that there are several potential alternative manufacturers who could manufacture RTB101 and rapalogs, such as everolimus or sirolimus, we may incur added costs and delays in identifying and qualifying

any such replacement. In addition, we typically order raw materials and services on a purchase order basis and do not enter into long-term dedicated capacity or minimum supply arrangements with any commercial manufacturer. There is no assurance that we will be able to timely secure needed supply arrangements on satisfactory terms, or at all. Our failure to secure these arrangements as needed could have a material adverse effect on our ability to complete the development of our product candidates or, to commercialize them, if approved. We may be unable to conclude agreements for commercial supply with third-party manufacturers, or may be unable to do so on acceptable terms. There may be difficulties in scaling up to commercial quantities and formulation of RTB101, alone or in combination with a rapalog, such as everolimus or sirolimus, and the costs of manufacturing could be prohibitive.

Even if we are able to establish and maintain arrangements with third-party manufacturers, reliance on third-party manufacturers entails additional risks, including:

- the failure of the third-party manufacturer to comply with applicable regulatory requirements and reliance on third-parties for manufacturing process development, regulatory compliance and quality assurance;
- manufacturing delays if our third-party manufacturers give greater priority to the supply of other products over our product candidates or otherwise do not satisfactorily perform according to the terms of the agreement between us;
- limitations on supply availability resulting from capacity and scheduling constraints of third-parties;
- the possible breach of manufacturing agreements by third-parties because of factors beyond our control;
- the possible termination or non-renewal of the manufacturing agreements by the third-party, at a time that is costly or inconvenient to us; and
- the possible misappropriation of our proprietary information, including our trade secrets and know-how.

If we do not maintain our key manufacturing relationships, we may fail to find replacement manufacturers or develop our own manufacturing capabilities, which could delay or impair our ability to obtain regulatory approval for our products. If we do find replacement manufacturers, we may not be able to enter into agreements with them on terms and conditions favorable to us and there could be a substantial delay before new facilities could be qualified and registered with the FDA and other foreign regulatory authorities.

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

Our failure, or the failure of our third-party manufacturers, to comply with applicable regulations could result in sanctions being imposed on us, including clinical holds, fines, injunctions, civil penalties, delays, suspension or withdrawal of approvals, seizures or voluntary recalls of product candidates, operating restrictions and criminal prosecutions, any of which could significantly affect supplies of our product candidates. The facilities used by our contract manufacturers to manufacture our product candidates must be evaluated by the FDA pursuant to inspections that will be conducted after we submit our NDA to the FDA. We do not control the manufacturing process of, and are completely dependent on, our contract manufacturing partners for compliance with cGMPs. If our contract manufacturers cannot successfully manufacture material that conforms to our specifications and the strict regulatory requirements of the FDA or others, we may not be able to secure and/or maintain regulatory approval for our product manufactured at these facilities. In addition, we have no control over the ability of our contract manufacturers to maintain adequate quality control, quality assurance and qualified personnel. If the FDA finds deficiencies or a comparable foreign regulatory authority does not approve these facilities for the manufacture of our product candidates or if it withdraws any such approval in the future, we may need to find alternative manufacturing facilities, which would significantly impact our ability to develop, obtain regulatory approval for or market our product candidates, if approved. Contract manufacturers may face manufacturing or quality control problems causing drug substance production and shipment delays or a situation where the contractor may not be able to maintain compliance with the applicable cGMP requirements. Any failure to comply with cGMP requirements or other FDA, EMA and comparable foreign regulatory requirements could adversely affect our clinical research activities and our ability to develop our product candidates and market our products, if approved.

The FDA and other foreign regulatory authorities require manufacturers to register manufacturing facilities. The FDA and corresponding foreign regulators also inspect these facilities to confirm compliance with cGMPs. Contract manufacturers may face manufacturing or quality control problems causing drug substance production and shipment delays or a situation where the contractor may not be able to maintain compliance with the applicable cGMP requirements. Any failure to comply with cGMP requirements or other FDA, EMA and comparable foreign regulatory requirements could adversely affect our clinical research activities and our ability to develop our product candidates and market our products following approval.

If any third-party manufacturer of our product candidates is unable to increase the scale of its production of our product candidates, and/or increase the product yield of its manufacturing, then our costs to manufacture the product may increase and commercialization may be delayed.

In order to produce sufficient quantities to meet the demand for clinical trials and, if approved, subsequent commercialization of RTB101, alone or in combination with a rapalog, such as everolimus or sirolimus, or any other product candidates that we may develop, our third party manufacturer will be required to increase its production and optimize its manufacturing processes while maintaining the quality of the product. The transition to larger scale production could prove difficult. In addition, if our third party manufacturer is not able to optimize its manufacturing process to increase the product yield for our product candidates, or if it is unable to produce increased amounts of our product candidates while maintaining the quality of the product, then we may not be able to meet the demands of clinical trials or market demands, which could decrease our ability to generate profits and have a material adverse impact on our business and results of operation.

We may need to maintain licenses for active ingredients from third parties to develop and commercialize some of our product candidates, which could increase our development costs and delay our ability to commercialize those product candidates.

Should we decide to use active pharmaceutical ingredients in any of our product candidates that are proprietary to one or more third parties, we would need to maintain licenses to those active ingredients from those third parties. If we are unable to gain or continue to access rights to these active ingredients prior to conducting preclinical toxicology studies intended to support clinical trials, we may need to develop alternate product candidates from these programs by either accessing or developing alternate active ingredients, resulting in increased development costs and delays in commercialization of these product candidates. If we are unable to gain or maintain continued access rights to the desired active ingredients on commercially reasonable terms or develop suitable alternate active ingredients, we may not be able to commercialize product candidates from these programs.

Use of third parties to conduct testing of our product candidates in tissues or animals may increase the risk that we will have unsuitable or invalidated data for regulatory submissions and approval.

We currently do not own or operate laboratory facilities in which to conduct preclinical testing of our product candidates in tissues or animals. Preclinical studies regulated by FDA, EMA and most other health authorities are governed by Good Laboratory Practices, or GLP. Additionally, studies involving animals may be subject to further regulation by institutional, private or government animal welfare authorities that may vary by territory. Studies involving human tissues may also be subject to institutional and government human subject privacy policies that may vary by territory. Third party vendors conducting tissue and/or animal studies on our behalf may be found to be in violation of one or more of these regulations or policies and may be subject to closure, censure or other penalties. In some cases, these penalties could materially impact the performance, availability, or validity of studies conducted on our behalf. Even in the absence of violations resulting in penalties, regulatory and other authorities may refuse to authorize the conduct or to accept the results of studies for regulatory or ethical reasons.

We enter into various contracts in the normal course of our business in which we indemnify the other party to the contract. In the event we have to perform under these indemnification provisions, it could have a material adverse effect on our business, financial condition and results of operations.

In the normal course of business, we periodically enter into academic, commercial, service, collaboration, licensing, consulting and other agreements that contain indemnification provisions. With respect to our academic and other research agreements, we typically indemnify the institution and related parties from losses arising from claims relating to the products, processes or services made, used, sold or performed pursuant to the agreements for which we have secured licenses, and from claims arising from our exercise of rights under the agreement. With respect to our commercial agreements, we indemnify our vendors from any third-party product liability claims that could result from the production, use or consumption of the product, as well as for alleged infringements of any patent or other intellectual property right by a third party.

Should our obligation under an indemnification provision exceed applicable insurance coverage or if we were denied insurance coverage, our business, financial condition and results of operations could be adversely affected. Similarly, if we are relying on a collaborator to indemnify us and the collaborator is denied insurance coverage or the indemnification obligation exceeds the applicable insurance coverage and does not have other assets available to indemnify us, our business, financial condition and results of operations could be adversely affected.

We may seek to establish collaborations and, if we are not able to establish them on commercially reasonable terms, we may have to alter our development and commercialization plans.

We may seek one or more collaborators for the development and commercialization of one or more of our product candidates. Likely collaborators may include large and mid-size pharmaceutical companies, regional and national pharmaceutical companies and biotechnology companies. In addition, if we are able to obtain regulatory approval for product candidates from foreign regulatory authorities, we may enter into collaborations with international biotechnology or pharmaceutical companies for the commercialization of such product candidates.

We face significant competition in seeking appropriate collaborators. Whether we reach a definitive agreement for a collaboration will depend, among other things, upon our assessment of the collaborator's resources and expertise, the terms and conditions of the proposed collaboration and the proposed collaborator's evaluation of a number of factors. Those factors may include the potential differentiation of our product candidate from competing product candidates, design or results of clinical trials, the likelihood of approval by the FDA, the EMA or comparable foreign regulatory authorities and the regulatory pathway for any such approval, the potential market for the product candidate, the costs and complexities of manufacturing and delivering the product to patients and the potential of competing products. The collaborator may also consider alternative product candidates or technologies for similar indications that may be available for collaboration and whether such a collaboration could be more attractive than the one with us for our product candidate. If we elect to increase our expenditures to fund development or commercialization activities on our own, we may need to obtain additional capital, which may not be available to us on acceptable terms or at all. If we do not have sufficient funds, we may not be able to further develop our product candidates or bring them to market and generate product revenue.

Collaborations are complex and time-consuming to negotiate and document. Further, there have been a significant number of recent business combinations among large pharmaceutical companies that have resulted in a reduced number of potential future collaborators. Any collaboration agreements that we enter into in the future may contain restrictions on our ability to enter into potential collaborations or to otherwise develop specified product candidates. We may not be able to negotiate collaborations on a timely basis, on acceptable terms, or at all. If we are unable to do so, we may have to curtail the development of the product candidate for which we are seeking to collaborate, reduce or delay its development program or one or more of our other development programs, delay its potential commercialization or reduce the scope of any sales or marketing activities, or increase our expenditures and undertake development or commercialization activities at our own expense.

If we enter into collaborations with third parties for the development and commercialization of our product candidates, our prospects with respect to those product candidates will depend in significant part on the success of those collaborations.

We may enter into collaborations for the development and commercialization of certain of our product candidates. If we enter into such collaborations, we will have limited control over the amount and timing of resources that our collaborators will dedicate to the development or commercialization of our product candidates. Our ability to generate revenues from these arrangements will depend on any future collaborators' abilities to successfully perform the functions assigned to them in these arrangements. In addition, any future collaborators may have the right to abandon research or development projects and terminate applicable agreements, including funding obligations, prior to or upon the expiration of the agreed upon terms.

Collaborations involving our product candidates pose a number of risks, including the following:

- collaborators have significant discretion in determining the efforts and resources that they will apply to these collaborations;
- collaborators may not perform their obligations as expected;

- collaborators may not pursue development and commercialization of our product candidates or may elect not to continue or renew development or commercialization programs, based on clinical trial results, changes in the collaborators' strategic focus or available funding or external factors, such as an acquisition, that divert resources or create competing priorities;

- collaborators may delay clinical trials, provide insufficient funding for a clinical trial program, stop a clinical trial or abandon a product candidate, repeat or conduct new clinical trials or require a new formulation of a product candidate for clinical testing;

- collaborators could independently develop, or develop with third parties, products that compete directly or indirectly with our product candidates;

- a collaborator with marketing and distribution rights to one or more products may not commit sufficient resources to the marketing and distribution of such product or products;

- disagreements with collaborators, including disagreements over proprietary rights, including trade secrets and intellectual property 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 intellectual property rights or may use our proprietary information in such a way as to invite litigation that could jeopardize or invalidate our intellectual property or proprietary information or expose us to potential litigation;

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

- collaborations may be terminated and, if terminated, may result in a need for additional capital to pursue further development or commercialization of the applicable product candidates.

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

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

We will require additional funds to complete the development and potential commercialization of RTB101 alone or in combination with a rapalog, such as everolimus or sirolimus and other product candidates. For some of our product candidates, we may decide to collaborate with pharmaceutical and biotechnology companies for the development and potential commercialization of those product candidates.

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

- the design or results of clinical trials;

- the likelihood of approval by the FDA or comparable foreign regulatory authorities;

- the potential market for the subject product candidate;

- the costs and complexities of manufacturing and delivering such product candidate to patients;

- the potential for competing products;

- our patent position protecting the product candidate, including any uncertainty with respect to our ownership of our technology or our licensor's ownership of technology we license from them, which can exist if there is a challenge to such ownership without regard to the merits of the challenge;

- the need to seek licenses or sub-licenses to third-party intellectual property; and

- industry and market conditions generally.

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

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

Risks Related to Employee Matters and Managing Growth

We only have a limited number of employees to manage and operate our business.

As of March 15, 2019, we had twenty-one full-time employees and no part-time employees. Our focus on the development of RTB101, alone or in combination with a rapalog, such as everolimus or sirolimus, requires us to optimize cash utilization and to manage and operate our business in a highly efficient manner. We cannot assure you that we will be able to hire and/or retain adequate staffing levels to develop RTB101, alone or in combination with a rapalog, such as everolimus or sirolimus, meet our obligations as a public company, run our operations and/or accomplish all of the objectives that we otherwise would seek to accomplish.

Cyber-attacks or other failures in our telecommunications or information technology systems, or those of our collaborators, contract research organizations, third-party logistics providers, distributors or other contractors or consultants, could result in information theft, data corruption and significant disruption of our business operations.

We, our collaborators, our CROs, third-party logistics providers, distributors and other contractors and consultants utilize information technology, or IT, systems and networks to process, transmit and store electronic information in connection with our business activities. As use of digital technologies has increased, cyber incidents, including deliberate attacks and attempts to gain unauthorized access to computer systems and networks, have increased in frequency and sophistication. These threats pose a risk to the security of our, our collaborators', our CROs', third-party logistics providers', distributors' and other contractors' and consultants' systems and networks, and the confidentiality, availability and integrity of our data. There can be no assurance that we will be successful in preventing cyber-attacks or successfully mitigating their effects. Similarly, there can be no assurance that our collaborators, CROs, third-party logistics providers, distributors and other contractors and consultants will be successful in protecting our clinical and other data that is stored on their systems. Any cyber-attack or destruction or loss of data could have a material adverse effect on our business and prospects. For example, the loss of clinical trial data from completed or ongoing clinical trials for any of our product candidates could result in delays in our development and regulatory approval efforts and significantly increase our costs to recover or reproduce the data. In addition, we may suffer reputational harm or face litigation or adverse regulatory action as a result of cyber-attacks or other data security breaches and may incur significant additional expense to implement further data protection measures.

We depend heavily on our executive officers, principal consultants and others and the loss of their services would materially harm our business.

Our success depends, and will likely continue to depend, upon our ability to hire, retain the services of our current executive officers, principal consultants and others, including Chen Schor, our president and chief executive officer, Joan Mannick, our chief medical officer, and Meredith Manning, our chief commercial officer. We have entered into employment agreements with Mr. Schor, Dr. Mannick, and Ms. Manning, but they may terminate their employment with us at any time. Although we do not have any reason to believe that we will lose the services of Mr. Schor, Dr. Mannick, and Ms. Manning in the foreseeable future, the loss of their services might impede the achievement of our research, development and commercialization objectives.

Our ability to compete in the biotechnology and pharmaceuticals industries depends upon our ability to attract and retain highly qualified managerial, scientific and medical personnel. Our industry has experienced a high rate of turnover of management personnel in recent years. Replacing executive officers or other key employees may be difficult and may take an extended period of time because of the limited number of individuals in our industry with the breadth of skills and experience required to develop, gain regulatory approval of and commercialize products successfully.

Competition to hire from this limited pool is intense, and we may be unable to hire, train, retain or motivate these additional key employees 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.

We rely on consultants and advisors, including scientific and clinical advisors, to assist us in formulating our research and development and commercialization strategy. Our consultants and advisors may be employed by other entities and may have commitments under consulting or advisory contracts with those entities that may limit their availability to us. If we are unable to continue to attract and retain highly qualified personnel, our ability to develop and commercialize our product candidates will be limited.

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

We are exposed to the risk that our employees, independent contractors, consultants, collaborators and contract research organizations may engage in fraudulent conduct or other illegal activity. Misconduct by those parties could include intentional, reckless and/or negligent conduct or disclosure of unauthorized activities to us that violates:

- FDA regulations or similar regulations of comparable non-U.S. regulatory authorities, including those laws requiring the reporting of true, complete and accurate information to such authorities;
- manufacturing standards;
- federal and state healthcare fraud and abuse laws and regulations and similar laws and regulations established and enforced by comparable non-U.S. regulatory authorities; and
- laws that require the reporting of financial information or data accurately.

Activities subject to these laws also involve the improper use or misrepresentation of information obtained in the course of clinical trials, creating fraudulent data in our preclinical studies or clinical trials or illegal misappropriation of product materials, which could result in regulatory sanctions and serious harm to our reputation. It is not always possible to identify and deter misconduct, and the precautions we take to detect and prevent this activity may not be effective in controlling unknown or unmanaged risks or losses or in protecting us from governmental investigations or other actions or lawsuits stemming from a failure to be in compliance with such laws, standards or regulations. Additionally, we are subject to the risk that a person or government could allege such fraud or other misconduct, even if none occurred. If any such actions are instituted against us, and we are not successful in defending ourselves or asserting our rights, those actions could have a significant impact on our business and results of operations, including the imposition of civil, criminal and administrative penalties, damages, monetary fines, possible exclusion from participation in Medicare, Medicaid and other federal healthcare programs, contractual damages, reputational harm, diminished profits and future earnings, and curtailment of our operations, any of which could have a material adverse effect on our ability to operate our business and our results of operations.

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

We expect to experience significant growth in the number of our employees and the scope of our operations, particularly in the areas of regulatory affairs and sales, marketing and distribution, as well as to support our public company operations. To manage these growth activities, we must continue to implement and improve our managerial, operational and financial systems, expand our facilities and continue to recruit and train additional qualified personnel. Our management may need to devote a significant amount of its attention to managing these growth activities. Moreover, our expected growth could require us to relocate to a different geographic area of the country. 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 or relocation of our operations, retain key employees, or identify, recruit and train additional qualified personnel. Our inability to manage the expansion or relocation of our operations effectively may result in weaknesses in our infrastructure, give rise to operational mistakes, loss of business opportunities, loss of employees and reduced productivity among remaining employees. Our expected growth could also require significant capital expenditures and may divert financial resources from other projects, such as the development of additional product candidates. If we are unable to effectively manage our expected growth, our expenses may increase more than expected, our ability to generate revenues could be reduced and we may not be able to implement our business strategy, including the successful commercialization of our product candidates.

Our current operations are concentrated primarily in a single location and any events affecting our headquarters may have material adverse consequences.

Our current operations are primarily located in our principal office in Boston, Massachusetts. Any unplanned event, such as flood, fire, explosion, earthquake, extreme weather condition, medical epidemics, power shortage, telecommunication failure or other natural or manmade accidents or incidents that result in us being unable to fully utilize the office may have a material adverse effect on our ability to operate our business, and have significant negative consequences on our financial and operating conditions. Loss of access to this office may result in increased costs, delays in the development of our product candidates or interruption of our business operations. As part of our risk management policy, we maintain insurance coverage at levels that we believe are appropriate for our business. However, in the event of an accident or incident at our office, our insurance coverage may not be sufficient to satisfy all of our damages and losses. If our office is unable to operate because of an accident or incident or for any other reason, even for a short period of time, any or all of our research and development programs may be harmed.

If we fail to maintain an effective system of internal control over financial reporting, we may not be able to accurately report our financial results or prevent fraud. As a result, stockholders could lose confidence in our financial and other public reporting, which would harm our business and the trading price of our common stock.

Effective internal controls over financial reporting are necessary for us to provide reliable financial reports and, together with adequate disclosure controls and procedures, are designed to prevent fraud. We currently have a limited number of employees performing our accounting functions, including monitoring and maintaining effective internal control over financial reporting. Any failure to implement required new or improved controls, or difficulties encountered in their implementation could cause us to fail to meet our reporting obligations. In addition, any testing by us conducted in connection with Section 404 of the Sarbanes-Oxley Act of 2002, or Section 404, or any subsequent testing by our independent registered public accounting firm, may reveal deficiencies in our internal controls over financial reporting that are deemed to be material weaknesses or that may require prospective or retroactive changes to our consolidated financial statements or identify other areas for further attention or improvement. Inferior internal controls could also cause investors to lose confidence in our reported financial information, which could have a negative effect on the trading price of our stock.

We will be required to disclose changes made in our internal controls and procedures on a quarterly basis and our management will be required to assess the effectiveness of these controls annually. However, for as long as we are an “emerging growth company” under the JOBS Act, our independent registered public accounting firm will not be required to attest to the effectiveness of our internal controls over financial reporting pursuant to Section 404. We could be an “emerging growth company” for up to five years. An independent assessment of the effectiveness of our internal controls over financial reporting could detect problems that our management’s assessment might not. Undetected material weaknesses in our internal controls over financial reporting could lead to financial statement restatements and require us to incur the expense of remediation.

Our disclosure controls and procedures may not prevent or detect all errors or acts of fraud.

Our disclosure controls and procedures are designed to reasonably assure that information required to be disclosed by us in reports we file or submit under the Exchange Act is accumulated and communicated to management, recorded, processed, summarized and reported within the time periods specified in the rules and forms of the SEC. We believe that any disclosure controls and procedures or internal controls and procedures, no matter how well conceived and operated, can provide only reasonable, not absolute, assurance that the objectives of the control system are met. These inherent limitations include the realities that judgments in decision-making can be faulty, and that breakdowns can occur because of simple error or mistake. Additionally, controls can be circumvented by the individual acts of some persons, by collusion of two or more people or by an unauthorized override of the controls. Accordingly, because of the inherent limitations in our control system, misstatements or insufficient disclosures due to error or fraud may occur and not be detected.

We have conducted and expect to continue to conduct our operations in jurisdictions outside of the United States, and such foreign operations subject us to additional risks.

A portion of our operations, including our clinical research and development efforts, have been undertaken outside of the United States, and we expect to continue to conduct a portion of our business in foreign countries. For example, we conducted our Phase 2b clinical trial across two hemispheres. In addition, we may utilize third party contract organizations, some of which may be located in foreign jurisdictions, for the conduct of our clinical trials, the manufacturing of our product candidates and the commercialization of our product candidates, if approved. Such operations subject us to additional risks related to international business operations, including:

- potentially reduced protection for intellectual property rights;
- price and currency exchange fluctuations;
- unexpected changes in tariffs, trade barriers and regulatory requirements;
- economic weakness, including inflation, or political instability in particular foreign economies and markets;
- workforce uncertainty in countries where labor unrest is more common than in the United States;
- difficulties in complying with tax, employment, immigration and labor laws for personnel living or traveling abroad;
- production shortages resulting from any events affecting a product candidate and/or finished drug product supply or manufacturing capabilities abroad;
- business interruptions resulting from geo-political actions, including war and terrorism, or natural disasters, including earthquakes, hurricanes, typhoons, floods and fires; and
- failure to comply with Office of Foreign Asset Control rules and regulations and the Foreign Corrupt Practices Act.

These and other risks may materially adversely affect our ability to conduct our business in international markets.

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

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

Risks Related to Our Common Stock

An active trading market for our common stock may not be sustained. If an active trading market is not sustained, our ability to raise capital in the future may be impaired.

Our shares began trading on The Nasdaq Global Select Market on January 26, 2018. Given the limited trading history of our common stock, there is a risk that an active trading market for our shares may not be sustained, which could put downward pressure on the market price of our common stock and thereby affect your ability to sell shares you purchased. An inactive trading market for our common stock may also impair our ability to raise capital to continue to fund our operations by selling shares and impair our ability to acquire other companies or technologies by using our shares as consideration.

The trading price of our common stock highly volatile, which could result in substantial losses for purchasers of our common stock. Securities class action or other litigation involving our company or members of our management team could also substantially harm our business, financial condition and results of operations.

Our stock price is highly volatile. The stock market in general and the market for smaller pharmaceutical and biotechnology companies in particular have experienced extreme volatility that has often been unrelated to the operating performance of particular companies. As a result of this volatility, you may not be able to sell your common stock at or above the purchase price and you may lose some or all of your investment. The market price for our common stock may be influenced by many factors, including:

- the success of existing or new competitive products or technologies;
- regulatory actions with respect to our product candidates or our competitors' products and product candidates;
- announcements by us or our competitors of significant acquisitions, strategic partnerships, joint ventures, collaborations or capital commitments;
- the timing and results of clinical trials of RTB101 alone or in combination with a rapalog, such as everolimus or sirolimus, and any other product candidates;
- commencement or termination of collaborations for our development programs;
- failure or discontinuation of any of our development programs;
- results of clinical trials of product candidates of our competitors;
- regulatory or legal developments in the United States and other countries;
- developments or disputes concerning patent applications, issued patents or other proprietary rights;
- the recruitment or departure of key personnel;
- the level of expenses related to any of our product candidates or clinical development programs;
- the results of our efforts to develop additional product candidates or products;
- actual or anticipated changes in estimates as to financial results or development timelines;
- announcement or expectation of additional financing efforts;
- sales of our common stock by us, our insiders or other stockholders;
- variations in our financial results or those of companies that are perceived to be similar to us;
- changes in estimates or recommendations by securities analysts, if any, that cover us;

- changes in the structure of healthcare payment systems;
- market conditions in the pharmaceutical and biotechnology sectors;
- general economic, industry and market conditions; and
- the other factors described in this "Risk Factors" section.

In the past, securities class action litigation has often been brought against a company following a decline in the market price of its securities. This risk is especially relevant for biopharmaceutical companies, which have experienced significant stock price volatility in recent years.

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

We are an emerging growth company, and, for as long as we continue to be an emerging growth company, we may choose to take advantage of exemptions from various reporting requirements applicable to other public companies but not to "emerging growth companies." We could remain an "emerging growth company" for up to five years following our IPO, or until the earliest of (1) the last day of the first fiscal year in which our annual gross revenue exceeds $1.07 billion, (2) the date that we become a "large accelerated filer" as defined in Rule 12b-2 under the Securities Exchange Act of 1934, which would occur if the market value of our common stock that is held by non-affiliates exceeds $700.0 million as of the last business day of our most recently completed second fiscal quarter or (3) the date on which we have issued more than $1.0 billion in non-convertible debt during the preceding three-year period. So long as we remain an "emerging growth company," we expect to avail ourselves of the exemption from the requirement that our independent registered public accounting firm attest to the effectiveness of our internal control over financial reporting under Section 404. When our independent registered public accounting firm is required to undertake an assessment of our internal control over financial reporting, the cost of our compliance with Section 404 will correspondingly increase. Moreover, if we are not able to comply with the requirements of Section 404 applicable to us in a timely manner, or if we or our independent registered public accounting firm identifies deficiencies in our internal control over financial reporting that are deemed to be material weaknesses, the market price of our stock could decline and we could be subject to sanctions or investigations by the SEC or other regulatory authorities, which would require additional financial and management resources.

We are also a "smaller reporting company," and the reduced disclosure requirements applicable to smaller reporting companies may make our common stock less attractive to investors.

We are considered a "smaller reporting company" under Rule 12b-2 of the Exchange Act. We are therefore entitled to rely on certain reduced disclosure requirements, such as an exemption from providing selected financial data and executive compensation information. These exemptions and reduced disclosures in our SEC filings due to our status as a smaller reporting company also mean our auditors are not required to review our internal control over financial reporting and may make it harder for investors to analyze our results of operations and financial prospects. We cannot predict if investors will find our common stock less attractive because we may rely on these exemptions. If some investors find our common stock less attractive as a result, there may be a less active trading market for our common stock and our common stock prices may be more volatile. We will remain a smaller reporting company until our public float exceeds $250 million or our annual revenues exceed $100 million with a public float greater than $700 million.

We have and will incur increased costs as a result of operating as a public company, and our management will be required to devote substantial time to new compliance initiatives and corporate governance practices.

As a public company, and particularly after we are no longer an "emerging growth company," we have and will incur significant legal, accounting and other expenses that we did not incur as a private company, including costs associated with public company reporting requirements. We have and will incur costs associated with relatively recently adopted corporate governance requirements, including requirements of the Securities and Exchange Commission, or SEC, and The Nasdaq Global Select Market. We expect these rules and regulations to increase our legal and financial compliance costs and to make some activities more time-consuming and costly. We also expect that these rules and regulations may make it more difficult and more expensive for us to obtain director and officer liability insurance and we may be required to accept reduced policy limits and coverage or incur substantially higher costs to obtain the same or similar coverage. As a result, it may be more difficult for us to attract and retain qualified individuals to serve on our board of directors or as executive officers.

We are currently evaluating and monitoring developments with respect to these rules, and we cannot predict or estimate the amount of additional costs we may incur or the timing of such costs. 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 are required to furnish a report by our management on our internal control over financial reporting beginning with this Annual Report on Form 10-K with the Securities and Exchange Commission, or the SEC. However, while we remain an emerging growth company, we will not be required to include an attestation report on internal control over financial reporting issued by our independent registered public accounting firm. To achieve compliance with Section 404 within the prescribed period, we have 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, engage outside consultants and adopt a detailed work plan to assess and document the adequacy of internal control over financial reporting. We will 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.

We have broad discretion over the use of our cash, cash equivalents, and marketable securities and may not use them effectively.

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

Future sales and issuances of our common stock or rights to purchase common stock, including pursuant to our equity incentive plans, could result in additional dilution of the percentage ownership of stockholders and could cause our stock price to fall.

The Company will need additional capital in the future to continue our planned operations in addition to the proceeds we received from our initial public offering in January 2018. To the extent we raise additional capital by issuing equity securities, our stockholders may experience substantial dilution. We may sell common stock, convertible securities or other equity securities in one or more transactions at prices and in a manner we determine from time to time. If we sell common stock, convertible securities or other equity securities in more than one transaction, investors may be materially diluted by subsequent sales. These sales may also result in material dilution to the Company’s existing stockholders, and new investors could gain rights superior to our existing stockholders.

On February 1, 2019, we filed a registration statement on Form S-3 (File No. 333-229499) with the SEC, which was declared effective on February 12, 2019 (the “Shelf Registration Statement”), in relation to the registration of common stock, preferred stock, warrants and/or units of any combination thereof for the purposes of selling, from time to time, our common stock, convertible securities or other equity securities in one or more offerings. The Shelf Registration Statement also registered for resale from time to time up to 12,445,646 shares of common stock held by the selling stockholders named therein. We also simultaneously entered into a Controlled Equity Offering Sales Agreement (the “Sales Agreement”) with SVB Leerink LLC and Cantor Fitzgerald & Co., (the “Sales Agents”), to provide for the offering, issuance and sale of up to an aggregate amount of $50.0 million of our common stock from time to time in “at-the-market” offerings under the Shelf Registration Statement and subject to the limitations thereof. The Company will pay to the Sales Agent cash commissions of 3.0 percent of the aggregate gross proceeds of sales of common stock under the Sales Agreement. Sales of common stock, convertible securities or other equity securities by us or our stockholders under the Shelf Registration Statement may represent a significant percentage of our common stock currently outstanding. If we or our stockholders sell, or the market perceives that we or our stockholders intend to sell, substantial amounts of our common stock under the Shelf Registration Statement or otherwise, the market price of our common stock could decline significantly.

In addition, sales of a substantial number of shares of our outstanding common stock in the public market could occur at any time. These sales, or the perception in the market that the holders of a large number of shares of common stock

intend to sell shares, could reduce the market price of our common stock. Persons who were our stockholders prior to our IPO continue to hold a substantial number of shares of our common stock that many of them are now able to sell in the public market. Significant portions of these shares are held by a relatively small number of stockholders. Sales by our stockholders of a substantial number of shares, or the expectation that such sales may occur, could significantly reduce the market price of our common stock.

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

We have never declared nor paid cash dividends on our capital stock. We currently plan to retain all of our future earnings, if any, to finance the operation, development and growth of our business. In addition, the terms of any future debt or credit agreements may preclude us from paying dividends. As a result, capital appreciation, if any, of our common stock will be your sole source of gain for the foreseeable future.

Our principal stockholders and management own a significant percentage of our stock and, if they choose to act together, will be able to control or exercise significant influence over matters subject to stockholder approval.

As of March 15, 2019, our executive officers, directors, five percent or greater stockholders and their affiliates beneficially own approximately 80.9 percent of our outstanding voting stock. These stockholders may have the ability to influence us through their ownership positions. These stockholders may be able to determine all matters requiring stockholder approval. For example, these stockholders, acting together, may be able to control elections of directors or approval of any merger, sale of assets or other major corporate transaction. This may prevent or discourage unsolicited acquisition proposals or offers for our common stock that you may believe are in your best interest as one of our stockholders.

Provisions in our corporate charter documents and under Delaware law may prevent or frustrate attempts by our stockholders to change our management or hinder efforts to acquire a controlling interest in us.

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

- establish a classified board of directors such that all members of the board are not elected at one time;
- allow the authorized number of our directors to be changed only by resolution of our board of directors;
- limit the manner in which stockholders can remove directors from the board;
- establish advance notice requirements for nominations for election to the board of directors or for proposing matters that can be acted on at stockholder meetings;
- require that stockholder actions must be effected at a duly called stockholder meeting and prohibit actions by our stockholders by written consent;
- limit who may call a special meeting of stockholders;
- authorize our board of directors to issue preferred stock without stockholder approval, which could be used to institute a “poison pill” that would work to dilute the stock ownership of a potential hostile acquirer, effectively preventing acquisitions that have not been approved by our board of directors; and
- require the approval of the holders of at least 66.7% 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 General Corporation Law of the State of Delaware, which prohibits a person who owns in excess of 15% of our outstanding voting stock from merging or combining with us for a period of three years after the date of the transaction in which the person acquired in excess of 15% of our outstanding voting stock, unless the merger or combination is approved in a prescribed manner. This could discourage, delay or prevent someone from acquiring us or merging with us, whether or not it is desired by, or beneficial to, our stockholders. This 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.

Our amended and restated bylaws provides that, unless we consent in writing to the selection of an alternative forum, the Court of Chancery of the State of Delaware will be the sole and exclusive forum for most legal actions between us and our stockholders, which could limit our stockholders' ability to obtain a favorable judicial forum for disputes with us or our directors, officers, employees or agents.

Our amended and restated bylaws specifies that, unless we consent in writing to the selection of an alternative forum, the Court of Chancery of the State of Delaware will be the sole and exclusive forum for (i) any derivative action or proceeding brought on behalf of the Company, (ii) any action asserting a claim of breach of a fiduciary duty owed by any director, officer or other employee of the Company to the Company or the Company's stockholders, (iii) any action asserting a claim arising pursuant to any provision of the Delaware General Corporation Law or the restated certificate of incorporation or amended and restated bylaws, or (iv) any action asserting a claim against the Company governed by the internal affairs doctrine. Any person or entity purchasing or otherwise acquiring any interest in shares of our capital stock shall be deemed to have notice of and to have consented to the provisions of our amended and restated bylaws described above.

We believe this provision benefits us by providing increased consistency in the application of Delaware law by chancellors particularly experienced in resolving corporate disputes, efficient administration of cases on a more expedited schedule relative to other forums and protection against the burdens of multi-forum litigation. However, the provision may have the effect of discouraging lawsuits against our directors, officers, employees and agents as it may limit any stockholder's ability to bring a claim in a judicial forum that such stockholder finds favorable for disputes with us or our directors, officers, employees or agents. The enforceability of similar choice of forum provisions in other companies' bylaws or certificates of incorporation has been challenged in legal proceedings, and it is possible that, in connection with any applicable action brought against us, a court could find the choice of forum provisions contained in our amended and restated bylaws to be inapplicable or unenforceable in such action. If a court were to find the choice of forum provision contained in our amended and restated bylaws to be inapplicable or unenforceable in an action, we may incur additional costs associated with resolving such action in other jurisdictions, which could adversely affect our business, financial condition or results of operations.

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

The trading market for our common stock will be influenced by the research and reports that industry or securities analysts publish about us or our business. If one or more of the analysts who cover us issues an adverse opinion about our company, our stock price would likely decline. If one or more of these analysts ceases research coverage of us or fails to regularly publish reports on us, we could lose visibility in the financial markets, which in turn could cause our stock price or trading volume to decline.

Item 1B. Unresolved Staff Comments.

Not applicable.

Item 2. Properties.

Our headquarters are located at 500 Boylston Street, 12th Floor, Boston, Massachusetts, where we occupy approximately 4,544 square feet of office space. This lease expires on February 28, 2021. We believe that this office is sufficient to meet our current needs and that suitable additional space will be available as and when needed.

Item 3. Legal Proceedings.

We are not currently subject to any material legal proceedings. From time to time, we may be subject to various legal proceedings and claims that arise in the ordinary course of our business activities. Although the results of litigation and claims cannot be predicted with certainty, as of the date of this report, we do not believe we are party to any claim or litigation the outcome of which, if determined adversely to us, would individually or in the aggregate be reasonably expected to have a material adverse effect on our business. Regardless of the outcome, litigation can have an adverse impact on us because of defense and settlement costs, diversion of management resources and other factors.

Item 4. Mine Safety Disclosures.

Not applicable.

PART II

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

Our common stock trades on The Nasdaq Global Select Market under the symbol "TORC". Trading of our common stock commenced on January 26, 2018, in connection with our initial public offering, or IPO. Prior to that time, there was no established public trading market for our common stock.

As of March 15, 2019, we had approximately 7 holders of record of our common stock. The actual number of holders of our common stock is greater than this number of record holders and includes stockholders who are beneficial owners, but whose shares are held in street name by brokers or held by other nominees. This number of holders of record also does not include stockholders whose shares may be held in trust by other entities.

Dividends

We have never declared or paid any cash dividends on our common stock. We currently intend to retain all available funds and any future earnings, if any, to fund the development and growth of our business. We do not expect to pay any cash dividends in the foreseeable future. Any future determination to pay dividends will be made at the discretion of our board of directors and will depend on various factors, including applicable laws, our results of operations, financial condition, future prospects, then applicable contractual restrictions and any other factors deemed relevant by our board of directors. Investors should not purchase our common stock with the expectation of receiving cash dividends.

Equity Compensation Plan

The information required by Item 5 of Form 10-K regarding equity compensation plans is incorporated herein by reference to Item 12 of Part III of this Annual Report on Form 10-K.

Purchase of Equity Securities by the Issuer and Affiliated Purchasers

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

Use of Proceeds from the Initial Public Offering

In January 2018, we completed our IPO pursuant to a registration statement on Form S-1 (File No. 333-222273), which was filed on December 29, 2017 and amended subsequently and declared effective on January 25, 2018. In the IPO, we issued and sold 6,516,667 shares of common stock (inclusive of 850,000 shares of common stock sold by us pursuant to the full exercise of an overallotment option granted to the underwriters in connection with the offering) at a public offering price of $15.00 per share, for aggregate gross proceeds of $97.8 million. The managing underwriters for the IPO were Merrill Lynch, Pierce, Fenner & Smith Incorporated, Leerink Partners LLC and Evercore ISI.

The aggregate proceeds received by the Company from the IPO were $89.4 million, net of underwriting discounts and commissions and estimated offering expenses payable by us. No offering expenses were paid directly or indirectly to any of our directors or officers (or their associates) or persons owning 10.0% or more of any class of our equity securities or to any other affiliates. As of December 31, 2018, we estimate that we have used approximately $36.2 million of cash and cash equivalents since our initial public offering to advance our product candidates through clinical trial programs and for working capital and general corporate purposes.

Information related to use of proceeds from registered securities is incorporated herein by reference to the "Use of Proceeds" section of the Company's final prospectus related to the IPO. There has been no material change in the planned use of proceeds from our IPO as described in our final prospectus.

Item 6. Selected Financial Data.

Information requested by this Item 6. Selected Financial Data is not applicable as we are electing scaled disclosure requirements available to Smaller Reporting Companies with respect to this Item 6.

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

You should read the following discussion and analysis of our financial condition and results of operations together with the section entitled "Selected Financial Data" and our consolidated financial statements and related notes included elsewhere in this Annual Report on Form 10-K. This discussion and other parts of this Annual Report on Form 10-K contain forward-looking statements that involve risks and uncertainties, such as our plans, objectives, expectations, intentions and beliefs. Our actual results could differ materially from those discussed in these forward-looking statements. Factors that could cause or contribute to such differences include, but are not limited to, those identified below and those discussed in the section entitled "Risk Factors" included elsewhere in this Annual Report on Form 10-K.

Overview

We are a clinical-stage biopharmaceutical company developing innovative medicines that target the biology of aging to prevent or treat age-related diseases with the potential to extend healthy lifespan. Our lead program selectively inhibits the target of rapamycin complex 1, or TORC1, an evolutionarily conserved pathway that contributes to the decline in function of multiple organ systems. Our lead product candidate, RTB101, is an oral, selective, and potent inhibitor of TORC1. RTB101 inhibits the phosphorylation of multiple targets downstream of TORC1. Inhibition of TORC1 has been observed to extend lifespan and healthspan in aging preclinical species and to enhance immune, neurologic and cardiac functions, suggesting potential benefits in several aging-related diseases. We licensed the worldwide rights to our TORC1 program, including RTB101 alone or in combination with everolimus, from Novartis International Pharmaceutical Ltd., or Novartis, in March 2017. In 2018, we reported results from our exploratory dose-ranging randomized, placebo-controlled Phase 2b clinical trial in 652 elderly patients at increased risk of RTI-associated morbidity and mortality defined as aged 85 and over, or 65-84 with one or more comorbidities including: asthma, COPD, T2DM, or current smoker. In this trial, RTB101 demonstrated a statistically significant and clinically meaningful reduction in the percentage of patients with one or more laboratory-confirmed RTIs during the 16-week treatment period compared to placebo, the primary endpoint of the study, with the 10 mg once daily dose. Greater TORC1 inhibition with RTB101 10 mg in combination with everolimus 0.1 mg did not meet the primary endpoint, suggesting that that less TORC1 inhibition with RTB101 10 mg once daily may have greater benefit in high-risk elderly patients. In addition, RTB101 demonstrated a statistically significant reduction in the incidence of laboratory-confirmed RTIs in the prespecified analysis of asthma patients 65 years and older treated with RTB101 10mg once daily as well as in laboratory-confirmed RTIs in the prespecified analysis of patients 85 years and older treated with RTB101 10mg once daily.

Since our inception in July 2016, we have devoted substantially all of our resources to: identifying, acquiring, and developing our product candidate portfolio; organizing and staffing our company; raising capital; developing manufacturing capabilities; conducting clinical trials; and providing general and administrative support for these operations. To date, we have primarily financed our operations through the issuance and sale of our redeemable convertible preferred stock and our initial public offering of our common stock, or IPO. In January 2018, we closed our IPO. We received aggregate net proceeds from the IPO of approximately $89.4 million, after deducting underwriting discounts and commissions and other offering expenses payable by us.

We have never generated revenue and have incurred significant net losses since inception. Our net losses were $37.6 million and $33.8 million for the years ended December 31, 2018 and 2017, respectively. As of December 31, 2018, we had an accumulated deficit of $71.4 million. Our net losses may fluctuate significantly from quarter to quarter and year to year. We expect to incur significant expenses and increasing operating losses for the foreseeable future. We anticipate that our expenses will increase substantially as we:

- invest significantly to further develop and seek regulatory approval for RTB101 alone or in combination with a rapalog, such as everolimus or sirolimus, including to advance our product candidate into a Phase 3 program;
- expand our pipeline of potential product candidates, including the initiation of at least one additional proof of concept trial in an additional indication;
- require the manufacture of larger quantities of our product candidates for clinical development and potentially commercialization;
- hire additional clinical, scientific, management and administrative personnel;

- ultimately establish a sales, marketing and distribution infrastructure or collaborate with third parties to commercialize any drugs for which we may obtain regulatory approval;

- maintain, expand and protect our intellectual property portfolio;

- acquire or in-license other assets and technologies; and

- add additional operational, financial and management information systems and processes to support our ongoing development efforts, any future manufacturing or commercialization efforts and our transition to operating as a public company.

We believe that our available funds will be sufficient to fund our operations at least into the second quarter of 2020. We have based this estimate on assumptions that may prove to be wrong, and we could utilize our available capital resources sooner than we currently expect. We do not expect to generate revenue from product sales unless and until we successfully complete development and obtain regulatory approval for a product candidate or enter into collaborative agreements with third parties, which we expect will take a number of years and the outcome of which is subject to significant uncertainty. Additionally, we currently use third parties such as contract research organizations, or CROs, and contract manufacturing organizations, or CMOs, to carry out our preclinical and clinical development activities and we do not yet have a sales organization. If we obtain regulatory approval for our product candidates, we expect to incur significant commercialization expenses related to product sales, marketing, manufacturing and distribution. To fund our current and future operating plans, we will need additional capital, which we may obtain through one or more equity offerings, debt financings or other third-party funding, including potential strategic alliances and licensing or collaboration arrangements. We may, however, be unable to raise additional funds or enter into such other arrangements when needed on favorable terms or at all. Our failure to raise capital or enter into such other arrangements as and when needed would have a negative impact on our financial condition and our ability to develop our current product candidates, or any additional product candidates, if developed. The amount and timing of our future funding requirements will depend on many factors, including the pace and results of our preclinical and clinical development efforts. We cannot assure you that we will ever be profitable or generate positive cash flow from operating activities.

Novartis License Agreement

On March 23, 2017, we entered into a license agreement with Novartis, pursuant to which we were granted an exclusive, field-restricted, worldwide license to certain intellectual property rights owned or controlled by Novartis, including patents, patent applications, proprietary information, know-how and other intellectual property, to develop, commercialize and sell one or more therapeutic products comprising RTB101 or RTB101 and everolimus in a fixed dose combination. Under the license agreement, we have been licensed a patent portfolio of ten patent families directed to composition of matter of RTB101 and its salts, formulations of everolimus and methods of using RTB101 and everolimus to enhance the immune response among others. The exclusive field for RTB101 under the license agreement is for the treatment, prevention and diagnosis of diseases and other conditions in all indications in humans and animals.

As initial consideration for the license, we issued Novartis Institutes for Biomedical Research, Inc., or NIBR, 2,587,992 shares of our Series A Preferred Stock.

The agreement may be terminated by either party upon a material breach of obligation by the other party that is not cured with 60 days after written notice. We may terminate the agreement in its entirety or on a product-by-product or country-by-country basis with or without cause with 60 days' prior written notice.

Novartis may terminate the portion of the agreement related to everolimus if we fail to use commercially reasonable efforts to research, develop and commercialize a product utilizing everolimus for a period of three years. Novartis may terminate the license agreement upon our bankruptcy, insolvency, dissolution or winding up.

As additional consideration for the license, we are required to pay up to an aggregate of $4.3 million upon the satisfaction of clinical milestones, up to an aggregate of $24 million upon the satisfaction of regulatory milestones for the first indication approved, and up to an aggregate of $18 million upon the satisfaction of regulatory milestones for the second indication approved. In addition, we are required to pay up to an aggregate of $125 million upon the satisfaction of commercial milestones, based on the amount of annual net sales. We are also required to pay tiered royalties ranging from a mid-single digit percentage to a low-teen digit percentage on annual net sales of products. These royalty obligations last on a product-by-product and country-by-country basis until the latest of (i) the expiration of the last valid claim of a Novartis patent covering a subject product, (ii) the expiration of any regulatory exclusivity for the subject product in a country, or (iii) the 10th anniversary of the first commercial sale in the country, and are subject to a reduction after the expiration of the last valid claim of a Novartis patent or the introduction of a generic equivalent of a product in a country.

Milestone payments to Novartis will be recorded as research and development expenses in our consolidated statements of operations and comprehensive loss once achievement of each associated milestone has occurred or the achievement is considered probable. In May 2017, we initiated a Phase 2b clinical trial for a first indication, triggering the first milestone payment under the agreement. Accordingly, we paid the related $0.3 million payment in May 2017. As of December 31, 2018, none of the remaining development milestones, regulatory milestones, sales milestones, or royalties had been reached. The remaining clinical milestones are the initiation of the Phase 3 clinical trials for the first indication and the initiation of each of the Phase 2 and Phase 3 clinical trials for the second indication. We also enter into contracts in the normal course of business with various third parties for preclinical research studies, clinical trials, testing and other services. These contracts generally provide for termination upon notice, and therefore we believe that our noncancelable obligations under these agreements are not material.

Financial Operations Overview

Revenue

We have not generated any revenue from the sale of our products, and we do not expect to generate any revenue unless and until we obtain regulatory approval of and commercialize RTB101, alone or in combination with a rapalog, such as everolimus or sirolimus.

Operating Expenses

Research and Development

Research and development expenses consist primarily of costs incurred for the development of our product candidates, which include:

- personnel costs, which include salaries, benefits and stock-based compensation expenses;
- expenses incurred under agreements with consultants, third-party contract organizations and investigative clinical trial sites that conduct research and development activities on our behalf;
- costs related to production of preclinical and clinical materials, including fees paid to contract manufacturers;
- laboratory and vendor expenses related to the execution of preclinical studies and clinical trials; and
- lab supplies and equipment used for internal research and development activities.

We have not provided program costs since inception because historically we have not tracked or recorded our research and development expenses on a program-by-program basis. We use our personnel and infrastructure resources across multiple research and development programs directed toward developing our TORC1 program and for identifying and developing product candidates. We manage certain activities such as contract research and manufacturing of RTB101 alone or in combination with a rapalog, such as everolimus or sirolimus, and our discovery programs through our third-party vendors, and do not track the costs of these activities on a program-by-program basis.

We expense all research and development costs in the periods in which they are incurred. Costs for certain development activities are recognized based on an evaluation of the progress to completion of specific tasks using information and data provided to us by our vendors and third-party service providers.

We expect our research and development expenses to increase substantially for the foreseeable future as we continue to invest in research and development activities related to developing our product candidates, including investments in manufacturing, as our programs advance into later stages of development and we continue to conduct clinical trials. The process of conducting the necessary clinical research to obtain regulatory approval is costly and time-consuming, and the successful development of our product candidates is highly uncertain. As a result, we are unable to determine the duration and completion costs of our research and development projects or when and to what extent we will generate revenue from the commercialization and sale of any of our product candidates.

Because of the numerous risks and uncertainties associated with product development, we cannot determine with certainty the duration and completion costs of the current or future preclinical studies and clinical trials or if, when, or to

what extent we will generate revenues from the commercialization and sale of our product candidates. We may never succeed in achieving regulatory approval for our product candidates. The duration, costs and timing of preclinical studies and clinical trials and development of our product candidates will depend on a variety of factors, including:

- successful completion of preclinical studies and Investigational New Drug-enabling studies;
- successful enrollment in, and completion of, clinical trials;
- receipt of regulatory approvals from applicable regulatory authorities;
- establishing commercial manufacturing capabilities or making arrangements with third-party manufacturers;
- obtaining and maintaining patent and trade secret protection and non-patent exclusivity;
- launching commercial sales of our product candidates, if and when approved, whether alone or in collaboration with others;
- acceptance of our product candidates, if and when approved, by patients, the medical community and third-party payors;
- effectively competing with other therapies and treatment options;
- a continued acceptable safety profile following approval;
- enforcing and defending intellectual property and proprietary rights and claims; and
- achieving desirable medicinal properties for the intended indications.

A change in the outcome of any of these factors could mean a significant change in the costs and timing associated with the development of our current and future preclinical and clinical product candidates. For example, if the FDA, or another regulatory authority were to require us to conduct clinical trials beyond those that we currently anticipate will be required for the completion of clinical development, or if we experience significant delays in execution of or enrollment in any of our preclinical studies or clinical trials, we could be required to expend significant additional financial resources and time on the completion of preclinical and clinical development.

General and Administrative

General and administrative expenses consist primarily of personnel costs, costs related to maintenance and filing of intellectual property, depreciation expense and other expenses for outside professional services, including legal, human resources, audit and accounting services. Personnel costs consist of salaries, benefits and stock-based compensation expense. We expect our general and administrative expenses to increase for the foreseeable future due to anticipated increases in headcount to advance our product candidates and as a result of operating as a public company, including expenses related to compliance with the rules and regulations of the Securities and Exchange Commission, The Nasdaq Global Select Market, additional insurance expenses, investor relations activities and other administration and professional services.

Other Income (Expense), Net

Other income (expense), net, consists of interest earned on cash, cash equivalents and marketable securities and non-cash changes in the fair value of the Tranche Rights liability associated with the redeemable convertible preferred stock.

Critical Accounting Polices and Estimates

Our management's discussion and analysis of our financial condition and results of operations is based on our consolidated financial statements, which have been prepared in accordance with United States generally accepted accounting principles, or U.S. GAAP. The preparation of these consolidated financial statements requires us to make estimates and assumptions that affect the reported amounts of assets and liabilities and the disclosure of contingent assets and liabilities at the date of the consolidated financial statements, as well as the expenses incurred during the reporting periods. Our estimates

are based on our historical experience and on various other factors that we believe are reasonable under the circumstances, the results of which form the basis for making judgments about the carrying value of assets and liabilities that are not readily apparent from other sources. Actual results may differ from these estimates under different assumptions or conditions. We believe that the accounting policies discussed below are critical to understanding our historical and future performance, as these policies relate to the more significant areas involving management's judgments and estimates.

Accrued Research and Development Costs

We accrue for estimated costs of research and development activities conducted by third-party service providers, which include the conduct of preclinical studies, clinical trials, and contract manufacturing activities. We record the estimated costs of research and development activities based upon the estimated amount of services provided, and include these costs in accrued liabilities in our consolidated balance sheets and within research and development expenses in our consolidated statements of operations and comprehensive loss. These costs are a significant component of our research and development expenses. We estimate the amount of work completed by third-party service providers through discussions with internal personnel and external service providers as to the progress or stage of completion of the services and the agreed-upon fee to be paid for such services. The majority of our service providers invoice in arrears for services performed, on a pre-determined schedule or when contractual milestones are met; however, some require advanced payments. We make significant judgments and estimates in determining the accrued balance in each reporting period based on the facts and circumstances known at that time. As actual costs become known, we adjust our accrued estimates. Although we do not expect our estimates to be materially different from amounts actually incurred, our understanding of the status and timing of services performed, the number of patients enrolled and the rate of patient enrollment may vary from our estimates and could result in us reporting amounts that are too high or too low in any particular period. Our accrued expenses are dependent, in part, upon the receipt of timely and accurate reporting from CROs, CMOs and other third-party service providers. To date, there have been no material differences from our accrued expenses to actual expenses.

Research and Development Costs

Research and development costs are expensed as incurred and consist of personnel costs, lab supplies and other costs, as well as fees paid to third parties to conduct research and development activities on our behalf.

Amounts incurred in connection with license agreements are also included in research and development expenses. We record payments made to outside vendors for services performed or goods being delivered for use in research and development activities as either prepaid expenses or accrued expenses, depending on the timing of when services are performed or goods are delivered.

Determination of Fair Value of Common and Preferred Shares and Tranche Rights Liabilities

Prior to the completion of our IPO, we were required to estimate the fair value of our common stock underlying our stock-based awards when performing the fair value calculations using the Black-Scholes option pricing model. The estimated fair value of our common and preferred shares were determined by the board of directors as of the grant date, with input from management, considering our most recently available third-party valuations of common and preferred shares and the board of directors' assessment of additional objective and subjective factors that it believed were relevant and which may have changed from the date of the most recent valuation through the date of the grant. These third-party valuations were performed in accordance with the guidance outlined in the American Institute of Certified Public Accountants' Accounting and Valuation Guide, *Valuation of Privately-Held-Company Equity Securities Issued as Compensation*, or the Practice Aid. Our common and preferred share valuations were prepared using either an option-pricing method, or OPM, or a probability-weighted expected return method, or PWERM, which uses a combination of market approaches and an income approach to estimate our enterprise value. The OPM treats common securities and preferred securities as call options on the total equity value of a company, with exercise prices based on the value thresholds at which the allocation among the various holders of a company's securities changes. Under this method, the common and preferred shares have value only if the funds available for distribution to stockholders are expected to exceed the value of the preferred security liquidation preference at the time of the liquidity event, such as a strategic sale or a merger. The PWERM is a scenario-based methodology that estimates the fair value of common and preferred shares based upon an analysis of future values for the enterprise, assuming various outcomes. The common and preferred share values are based on the probability-weighted present value of expected future investment returns considering each of the possible outcomes available as well as the rights of each class of common and preferred securities. The future value of the common and preferred shares under each outcome is discounted back to the valuation date at an appropriate risk-adjusted discount rate and probability weighted to arrive at an indication of value for the common and preferred shares. The estimated fair value of the Tranche Rights was determined using the difference between the total purchase price of our preferred stock and the total fair value of the preferred stock using a risk-adjusted forward contract model.

Stock-Based Compensation Expense

We recognize equity-based compensation expense for awards of equity instruments to employees and non-employees based on the grant date fair value of those awards in accordance with the Financial Accounting Standards Board, or FASB, Accounting Standards Codification, or ASC, Topic 718, *Stock Compensation*, or ASC 718. ASC 718 requires all equity-based compensation awards to employees and non-employee directors, including grants of restricted shares and stock options, to be recognized as expense in the consolidated statements of operations and comprehensive loss based on their grant date fair values. We estimate the fair value of stock options using the Black-Scholes option pricing model. We use the value of our common stock to determine the fair value of restricted shares.

We account for restricted stock and common stock options issued to non-employees under FASB ASC Topic 505-50, *Equity-Based Payments to Non-Employees*, or ASC 505-50. As such, the value of such options is periodically remeasured and income or expense is recognized over their vesting terms. Compensation cost related to awards with service-based vesting schedules is recognized using the straight-line method. We determine the fair value of the restricted stock and common stock granted to non-employees as either the fair value of the consideration received or the fair value of the equity instruments issued.

The Black-Scholes option pricing model requires the input of certain subjective assumptions, including (i) the expected volatility, (ii) the expected term of the award, (iii) the risk-free interest rate and (iv) the expected dividend yield. Due to the lack of a public market for the trading of our common stock and a lack of company-specific historical and implied volatility data, we have based our estimate of expected volatility on the historical volatility of a group of similar companies that are publicly traded. The historical volatility is calculated based on a period of time commensurate with the expected term assumption. The group of representative companies has characteristics similar to us, including stage of product development and focus on the life science industry. We use the simplified method, which is the average of the final vesting tranche date and the contractual term, to calculate the expected term for options granted to employees as we do not have sufficient historical exercise data to provide a reasonable basis upon which to estimate the expected term. For options granted to non-employees, we utilize the contractual term of the arrangement as the basis for the expected term assumption. The risk-free interest rate is based on a treasury instrument whose term is consistent with the expected term of the stock options. We use an assumed dividend yield of zero as we have never paid dividends and have no current plans to pay any dividends on our common stock.

The following table presents the assumptions used to estimate the fair value of options granted:

	Year Ended December 31,	
	2018	2017
Employees:		
Fair value of common stock	$8.57 - $15.45	$0.79 - $9.33
Expected term (in years)	5.8 - 6.2	5.9 - 6.2
Expected volatility	75.9% - 90.6%	74.4% - 74.5%
Risk-free interest rate	2.4% - 3.1%	1.9% - 2.2%
Expected dividend yield	0.0%	0.0%
Non-employees:		
Fair value of common stock	$8.62 - $15.45	$0.79 - $10.28
Expected term (in years)	10.0 - 8.50	10.0 - 9.4
Expected volatility	78.0% - 91.2%	74.6% - 77.0%
Risk-free interest rate	2.7% - 3.1%	2.3% - 2.4%
Expected dividend yield	0.0%	0.0%

There were no stock options granted during the period from July 5, 2016 (inception) to December 31, 2016.

For the years ended December 31, 2018 and 2017 and the period from July 5, 2016 (inception) through December 31, 2016, stock-based compensation expense was $2.8 million, $0.5 million and $0, respectively. As of December 31, 2018, we had $7.8 million of total unrecognized stock-based compensation expense, which we expect to recognize over a weighted-average period of 3.17 years.

The following table presents the grant dates of common shares, stock options, and awards that we granted from July 5, 2016 (inception) through January 25, 2018 along with the corresponding purchase or exercise price for each grant and

our estimate of the fair value per share of our common stock on each grant date, which we utilized to calculate stock-based compensation expense:

Grant Date	Type of Award	Number of Shares	Purchase or Exercise Price per Share	Estimate of Common Stock Fair Value per Share on Grant Date
7/11/2016	Restricted common shares	3,772,726	$ 0.0001	$ 0.0001
3/1/2017	Common shares	1,886,363	$ 0.0001	$ 0.0001
6/12/2017	Options	101,948	$ 0.79	$ 0.79
9/14/2017	Options	9,372	$ 1.00	$ 1.00
12/5/2017	Options	84,349	$ 9.33	$ 9.33
1/12/2018	Options	111,320	$ 13.17	$ 13.17

Determination of the Fair Value of Common Stock on Grant Dates

Prior to the completion of our IPO, we were required to estimate the fair value of our common stock underlying our stock-based awards when performing the fair value calculations using the Black-Scholes option pricing model. The fair values of the shares of common stock underlying our share-based awards were estimated on each grant date by our board of directors. The restricted common shares were granted to non-employees and subsequently were marked to market at each reporting date. On April 4, 2017, the non-employees became employees of our company and the fair value of the remaining unvested shares was fixed at $0.79 per share. In order to determine the fair value of our common stock our board of directors considered, among other things, contemporaneous valuations of our common stock prepared by an independent third-party valuation specialist in accordance with the guidance provide by the Practice Aid.

Given the absence of a public trading market for our common stock prior to the IPO, our board of directors exercised their judgment and considered a number of objective and subjective factors to determine the best estimate of the fair value of our common stock, including our stage of development; progress of our research and development efforts; the rights, preferences and privileges of our preferred stock relative to those of our common stock; equity market conditions affecting comparable public companies; the lack of marketability of our common stock; and valuations obtained from issuance of our preferred stock to unrelated parties.

We performed common stock valuations, with the assistance of an independent third-party valuation specialist, as of March 23, 2017, September 8, 2017, November 30, 2017 and December 31, 2017, which resulted in valuations of our common stock of $0.79, $1.00, $9.33 and $13.17, respectively. In conducting the valuations, the independent third-party valuation specialist considered all objective and subjective factors that it believed to be relevant for each valuation conducted in accordance with the Practice Aid, including our best estimate of our business condition, prospects and operating performance at each valuation date. Other significant factors included:

- the prices of our preferred stock sold to outside investors in arm’s length transactions, and the rights, preferences and privileges of our preferred stock as compared to those of our common stock, including the liquidation preferences of our preferred stock;
- our stage of development and business strategy and the material risks related to our business and industry;
- the valuation of publicly traded companies in the life sciences and biotechnology sectors, as well as recently completed mergers and acquisitions of guideline companies;
- our results of operations and financial position;
- the composition of, and changes to, our management team and board of directors;
- the lack of liquidity of our common stock;
- any external market conditions affecting the life sciences and biotechnology industry sectors;

- the likelihood of achieving a liquidity event for the holders of our common stock and stock options, such as an IPO or a sale of our company, given prevailing market conditions; and

- the state of the IPO market for similarly situated privately held life sciences companies.

The dates of our contemporaneous valuations have not always coincided with the dates of our stock option grants. In determining the exercise prices of the stock options set forth in the table above, our board of directors considered, among other things, the most recent valuation of our common stock and their assessment of additional objective and subjective factors that were relevant as of the grant dates. The additional factors considered when determining whether any changes in the fair value of our common stock had occurred between the most recent valuation and the grant dates included our stage of research and development, our operating and financial performance and current business conditions.

The estimates of fair value of our common stock are highly complex and subjective. There are significant judgments and estimates inherent in the determination of the fair value of our common stock. These judgments and estimates include assumptions regarding our future operating performance, the time to completing an IPO or other liquidity event, the related valuations associated with these events, and the determinations of the appropriate valuation methods at each valuation date. The assumptions underlying these valuations represent management's best estimates, which involve inherent uncertainties and the application of management judgment. If we had made different assumptions, our stock-based compensation expense, net loss and net loss per share applicable to common stockholders could have been materially different.

Results of Operations

Comparison of the Years Ended December 31, 2018 and 2017

	Year Ended December 31,	
	2018	2017
	(In thousands)	
Operating expenses:		
Research and development	$ 31,065	$ 16,839
General and administrative	8,640	2,043
Total operating expenses	39,705	18,882
Loss from operations	(39,705)	(18,882)
Other income (expense), net	2,117	(14,896)
Loss before income taxes	(37,588)	(33,778)
Income tax expense	(26)	—
Net loss	$ (37,614)	$ (33,778)

Research and Development

Research and development expenses increased to $31.1 million for the year ended December 31, 2018, and were primarily attributable to $18.0 million of costs from third-party contract organizations and investigative clinical trial sites related to clinical trials, including the Phase 2b clinical trial, $7.4 million of costs related to preclinical studies and the production of preclinical and clinical materials, $1.2 million of costs related to external consulting incurred to supplement our research and development personnel, and $4.5 million of personnel costs, including stock-based compensation. Research and development expenses were $16.8 million for the year ended December 31, 2017, and were primarily attributable to $3.9 million of costs associated with our license agreement with Novartis, including the license of the intellectual property in exchange for Series A preferred stock, $10.0 million of costs related to clinical trials, including the Phase 2b clinical trial, $1.3 million of costs related to contract research and supplies, $0.6 million of costs related to external consulting incurred to supplement our research and development personnel, and $1.0 million of personnel costs, including stock-based compensation.

General and Administrative

General and administrative expenses increased to $8.6 million for the year ended December 31, 2018, and were primarily attributable to $5.2 million of personnel, including stock-based compensation, and $3.4 million of professional services fees, including costs related to intellectual property, legal and filing costs, accounting costs, insurance, and external consulting costs incurred to supplement our personnel. General and administrative expenses were $2.0 million for the year ended December 31, 2017, and were primarily attributable to $1.0 million of personnel, including stock-based compensation, and $1.0 million of professional services fees, including costs related to intellectual property, legal and filing costs, accounting costs, and external consulting costs incurred to supplement our personnel.

Other Income (Expense), Net

Other income, net was $2.1 million for the year ended December 31, 2018, and primarily consisted of interest income. Other expense, net was $14.9 million for the year ended December 31, 2017, and entirely consisted of the change in fair value of our Tranche Rights related to our redeemable convertible preferred stock.

Comparison of the Year Ended December 31, 2017 and the period from July 5, 2016 (Inception) through December 31, 2016

	Year Ended December 31, 2017	July 5, 2016 (inception) through December 31, 2016
	(In thousands)	
Operating expenses:		
Research and development	$ 16,839	$ —
General and administrative	2,043	1
Total operating expenses	18,882	1
Loss from operations	(18,882)	(1)
Other expense, net	(14,896)	—
Net loss	$ (33,778)	$ (1)

Research and Development

Research and development expenses increased to $16.8 million for the year ended December 31, 2017, and were primarily attributable to $3.9 million of costs associated with our license agreement with Novartis, including the license of the intellectual property in exchange for Series A preferred stock, $1.3 million of costs related to contract research and supplies, $10.0 million of costs related to clinical trials, including the Phase 2b clinical trial, $0.6 million of costs related to external consulting incurred to supplement our research and development personnel, and $1.0 million of personnel costs, including stock-based compensation. We did not have any research and development expenses for the period from July 5, 2016 (inception) through December 31, 2016, as our primary operations did not commence until March 23, 2017, when we acquired our license to develop, make, use, and sell products incorporating RTB101 alone or in combination with everolimus.

General and Administrative

General and administrative expenses increased to $2.0 million for the year ended December 31, 2017, and were primarily attributable to $1.0 million of personnel, including stock-based compensation, and $1.0 million of professional services fees, including costs related to intellectual property, legal and filing costs, accounting costs, and external consulting costs incurred to supplement our personnel. General and administrative expenses were $1,000 for the period from July 5, 2016 (inception) through December 31, 2016 and consisted entirely of registration and filing fees related to our incorporation.

Other Expense, Net

Other expense, net was $14.9 million for the year ended December 31, 2017, and entirely consisted of the change in fair value of our tranche rights related to our redeemable convertible preferred stock. Other expense, net was $0 for the period from July 5, 2016 (inception) through December 31, 2016.

Liquidity, Capital Resources and Plan of Operations

In January 2018, we closed our IPO and received aggregate net proceeds of approximately $89.4 million, after deducting underwriting discounts and commissions and other offering expenses payable by us.

Since inception, we have not generated any revenue from any sources, including from product sales, and have incurred significant operating losses and negative cash flows from our operations. We have funded our operations to date primarily with proceeds from our IPO and the sale of shares of our redeemable convertible preferred stock. As of December 31, 2018, we had $108.0 million in cash, cash equivalents and marketable securities and an accumulated deficit of $71.4 million.

Our primary use of cash has been to fund operating expenses, which consist of research and development and general and administrative expenditures. Cash used to fund operating expenses is impacted by the timing of when we pay these expenses, as reflected in the change in our outstanding accounts payable and accrued expenses.

Based upon our current operating plan, we believe that our existing cash, cash equivalents and marketable securities will enable us to fund our operating expenses and capital expenditure requirements at least into the second quarter of 2020. We have based this estimate on assumptions that may prove to be wrong, and we could utilize our available capital resources sooner than we currently expect. We will continue to require additional financing to advance our current product candidate through clinical development, to develop, acquire or in-license other potential product candidates and to fund operations for the foreseeable future. Furthermore, with the closing of our IPO, we have begun to incur additional costs associated with operating as a public company. Accordingly, we will continue to seek funds through equity or debt financings, collaborative or other arrangements, or through other sources of financing. Adequate additional funding may not be available to us on acceptable terms, or at all. Any failure to raise capital as and when needed could have a negative impact on our financial condition and on our ability to pursue our business plans and strategies.

Further, our operating plans may change, and we may need additional funds to meet operational needs and capital requirements for clinical trials and other research and development activities. We currently have no credit facility or committed sources of capital. Because of the numerous risks and uncertainties associated with the development and commercialization of our product candidates, we are unable to estimate the amounts of increased capital outlays and operating expenditures associated with our current and anticipated product development programs.

If we need to raise additional capital to fund our operations, funding may not be available to us on acceptable terms, or at all. If we are unable to obtain adequate financing when needed, we may have to delay, reduce the scope of or suspend one or more of our clinical trials, research and development programs or commercialization efforts. We may seek to raise any necessary additional capital through a combination of public or private equity offerings, debt financings, and collaborations or licensing arrangements. If we do raise additional capital through public or private equity offerings, the ownership interest of our existing stockholders will be diluted, and the terms of these securities may include liquidation or other preferences that adversely affect our stockholders' rights. If we raise additional capital through debt financing, we may be subject to covenants limiting or restricting our ability to take specific actions, such as incurring additional debt, making capital expenditures or declaring dividends. If additional funding is required, there can be no assurance that additional funds will be available to us on acceptable terms on a timely basis, if at all. If we are unable to raise capital, we will need to curtail planned activities to reduce costs. Doing so will likely have an unfavorable effect on our ability to execute our business plans.

The following table summarizes our cash flows for the periods indicated:

	Year Ended December 31,		
	2018	2017	2016
	(In thousands)		
Net cash used in operating activities	$ (35,534)	$ (10,985)	$ —
Net cash used in investing activities	(100,716)	(44)	—
Net cash provided by financing activities	89,943	64,378	—
Net (decrease) increase in cash and cash equivalents	$ (46,307)	$ 53,349	$ —

Cash Flows from Operating Activities

Cash used in operating activities for the year ended December 31, 2018 was $35.5 million, consisting of a net loss of $37.6 million adjusted for noncash items including stock-based compensation expense of $2.8 million and accretion on marketable securities of $0.7 million. The change in our net operating assets and liabilities for the year ended December 31, 2018 were due primarily to an increase in accounts payable and accrued liabilities of $0.6 million primarily due to increased clinical activities, which were partially offset by an increase in prepaid expenses and other current assets of $0.6 million due to prepayments for our research and development activities. Cash used in operating activities for the year ended December 31, 2017 was $11.0 million, consisting of a net loss of $33.8 million adjusted for noncash items including the loss resulting from the change in fair value of the tranche rights of $14.9 million, stock-based compensation expense of $0.5 million and expense related to the acquisition of intellectual property of $3.2 million. The change in our net operating assets and liabilities were due primarily to an increase in accounts payable of $1.4 million as a result of payment timing and an increase in accrued liabilities of $3.7 million primarily due to increased clinical activities, which were partially offset by an increase in prepaid expenses and other current assets of $0.9 million due to prepayments for our research and development activities. No cash was used in operating activities for the period from July 5, 2016 (inception) through December 31, 2016.

Cash Flows from Investing Activities

Cash used in investing activities for the year ended December 31, 2018 was $100.7 million and consisted of $107.9 million for the purchases of marketable securities and $0.3 million for the purchases of property and equipment, partially offset by $7.5 million from the maturities of marketable securities. Cash used in investing activities for the year ended December 31, 2017 was $44,000 and consisted of the purchases of property and equipment. No cash was used in investing activities for the period from July 5, 2016 (inception) through December 31, 2016.

Cash Flows from Financing Activities

Cash provided by financing activities for the year ended December 31, 2018 was $89.9 million from the proceeds from the IPO, net of issuance costs paid in 2018. Cash provided by financing activities for the year ended December 31, 2017 was $64.4 million primarily from the issuance of redeemable convertible preferred stock partially offset by costs incurred in connection with the IPO. No cash was provided by financing activities for the period from July 5, 2016 (inception) through December 31, 2016.

Contractual Obligations and Other Commitments

In January 2018, we entered into a multi-year agreement to lease office space in Boston, Massachusetts under an operating lease agreement. Payments under the contract commenced in March 2018. The following table summarizes our outstanding contractual obligations as of payment due date by period at December 31, 2018 (in thousands).

Total	Less than 1 Year	1 to 3 Years	3 to 5 Years	More than 5 Years
$ 506	$ 231	$ 275	$ —	$ —

In March 2017, we entered into a license Agreement with Novartis. See "—Overview—Novartis License Agreement." Amounts owed under this license agreement are not included in the table above as they were considered a contingent payment as of December 31, 2018.

We enter into contracts in the normal course of business with CROs and CMOs to assist in the performance of our research and development activities and other services and products for operating purposes. These contracts generally provide for termination upon notice, and therefore are cancelable contracts and not included in the table of contractual obligations and commitments.

Net Operating Loss Carryforwards

As of December 31, 2018, we had federal and state net operating loss carryforwards of $47.3 million and $49.4 million, respectively, which begin to expire in various amounts in 2036. As of December 31, 2018, we also had federal research and development tax credit carryforwards of $0.9 million, which begin to expire in 2037. These net operating loss and tax credit carryforwards could expire unused and be unavailable to offset future income tax liabilities. Federal net operating loss carryforwards generated after December 31, 2017 are not subject to expiration. In addition, in general, under

Sections 382 and 383 of the Internal Revenue Code of 1986, as amended, or the Code, a corporation that undergoes an "ownership change" is subject to limitations on its ability to utilize its pre-change net operating losses or tax credits, or NOLs or credits, to offset future taxable income or taxes. For these purposes, an ownership change generally occurs where the aggregate stock ownership of one or more stockholders or groups of stockholders who owns at least 5% of a corporation's stock increases its ownership by more than 50 percentage points over its lowest ownership percentage within a specified testing period. Our existing NOLs or credits may be subject to limitations arising from previous ownership changes, and if we undergo an ownership change in connection with or after our IPO, our ability to utilize NOLs or credits could be further limited by Sections 382 and 383 of the Code. In addition, future changes in our stock ownership, many of which are outside of our control, could result in an ownership change under Sections 382 and 383 of the Code. Our NOLs or credits may also be impaired under state law. Accordingly, we may not be able to utilize a material portion of our NOLs or credits. We have not completed a study to determine whether our IPO, our most recent private placement of our Series B preferred stock and other transactions that have occurred over the past three years may have triggered an ownership change limitation. If we determine that an ownership change has occurred and our ability to use our historical NOLs or credits is materially limited, it would harm our future operating results by effectively increasing our future tax obligations. We have not performed an ownership change analysis.

Furthermore, our ability to utilize our NOLs or credits is conditioned upon our attaining profitability and generating U. S. federal and state taxable income. As described above under "Risk Factors—Risks Related to our Financial Position and Need for Additional Capital," we have incurred significant net losses since our inception and anticipate that we will continue to incur significant losses for the foreseeable future; and therefore, we do not know whether or when we will generate the U.S. federal or state taxable income necessary to utilize our NOL or credit carryforwards that are subject to limitation by Sections 382 and 383 of the Code.

Off-Balance Sheet Arrangements

We have not entered into any off-balance sheet arrangements and do not have any holdings in variable interest entities.

JOBS Act Accounting Election

In addition to being a smaller reporting company, we are an "emerging growth company," as defined in the Jumpstart Our Business Startups Act of 2012, or the JOBS Act. As an emerging growth company, we may take advantage of specified reduced disclosure and other requirements that are otherwise applicable generally to public companies. We would cease to be an emerging growth company on the date that is the earliest of: (i) the last day of the fiscal year in which we have total annual gross revenues of $1.07 billion or more; (ii) December 31, 2023; (iii) the date on which we have issued more than $1.0 billion in nonconvertible debt during the previous three years; or (iv) the date on which we are deemed to be a large accelerated filer under the rules of the SEC.

Recently Issued and Adopted Accounting Pronouncements

In May 2017, the FASB issued ASU 2017-09, *Compensation—Stock Compensation* (Topic 718): Scope of Modification Accounting, or ASU 2017-09. ASC 2017-09 provides guidance about which changes to the terms or conditions of a share-based payment award require an entity to apply modification accounting in Topic 718. The guidance is effective for annual periods beginning after December 15, 2017, with early adoption permitted, including adoption in any interim period for which financial statements have not yet been issued. We are currently evaluating the potential effects of adopting the provisions of ASU 2017-09. We adopted the provisions of ASU 2017-09 on January 1, 2018. No modifications of share-based payment awards have occurred as of December 31, 2018.

In February 2016, the FASB issued ASU 2016-02, *Leases* ("ASU 2016-02"), which requires a lessee to recognize a right-of-use asset and a lease liability for operating leases, initially measured at the present value of the future lease payments, in the balance sheet. ASU 2016-02 also requires a lessee to recognize a single lease cost, calculated so that the cost of the lease is allocated over the lease term, generally on a straight-line basis. This new guidance is effective for fiscal years beginning after December 15, 2019. Early adoption is permitted. We are currently evaluating the potential effects of adopting the provisions of ASU 2016-02 to our consolidated financial statements.

In November 2016, the FASB issued ASU 2016-18, *Statement of Cash Flows*, or ASU 2016-18, which requires that amounts generally described as restricted cash and restricted cash equivalents should be included with cash and cash equivalents when reconciling the beginning-of-period and end-of-period total amounts shown on the statement of cash flows.

ASU 2016-18 is effective for fiscal years beginning after December 15, 2018 and should be applied using a retrospective transition method to each period presented. Early adoption is permitted. We do not expect the impact of ASU 2016-18 to be material to our consolidated financial statements.

In July 2017, the FASB issued ASU 2017-11, *Accounting for Certain Financial Instruments with Down Round Features*, or ASU 2017-11, which updates the guidance related to the classification analysis of certain equity-linked financial instruments (or embedded features) with down round features. Under ASU 2017-11, a down round feature no longer precludes equity classification when assessing whether the instrument is indexed to an entity's own stock. As a result, a freestanding equity-linked financial instrument (or embedded conversion option) no longer would be accounted for as a derivative liability at fair value as a result of the existence of a down round feature. For freestanding equity classified financial instruments, the amendments require entities that present earnings per share (EPS) in accordance with Topic 260 to recognize the effect of the down round feature when it is triggered. That effect is treated as a dividend and as a reduction of income available to common shareholders in basic EPS. ASU 2017-11 is effective for public entities for all annual and interim periods beginning after December 15, 2019. Early adoption is permitted. We do not expect the impact of ASU 2017-11 will be material to our consolidated financial statements.

In June 2018, the FASB issued ASU No. 2018-07, *Compensation – Stock Compensation (Topic 718), Improvements to Nonemployee Share-Based Payment Accounting* ("ASU 2018-07"), which intends to simplify aspects of share-based compensation issued to non-employees by making the guidance consistent with the accounting for employee share-based compensation. For public entities, ASU 2018-07 is required to be adopted for annual periods beginning after December 15, 2018, including interim periods within those fiscal years. For non-public entities and emerging growth companies that choose to take advantage of the extended transition period, ASU 2018-07 is effective for annual periods beginning after December 15, 2019. Early adoption is permitted for all entities but no earlier than the Company's adoption of *Revenue from Contracts with Customers* ("ASC 606"). We are currently evaluating the impact that the adoption of ASU 2018-07 will have on our consolidated financial statements.

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

We are exposed to market risk related to changes in interest rates. As of December 31, 2018, we had cash, cash equivalents and marketable securities of $108.0 million, primarily comprised of money market mutual funds consisting of U.S. government-backed securities. Our primary exposure to market risk is interest rate sensitivity, which is affected by changes in the general level of U.S. interest rates, particularly because our investments are in short-term securities. Our available for sale securities are subject to interest rate risk and will fall in value if market interest rates increase. Due to the short-term duration of our investment portfolio and the low risk profile of our investments, an immediate 100 basis point change in interest rates would not have a material effect on the fair market value of our portfolio.

We contract with CROs and contract manufacturers globally. We may be subject to fluctuations in foreign currency rates in connection with certain of these agreements. Transactions denominated in currencies other than the United States dollar are recorded based on exchange rates at the time such transactions arise. We have not engaged in the hedging of our foreign currency transactions to date, we are evaluating the costs and benefits of initiating such a program and may in the future hedge selected significant transactions denominated in currencies other than the U.S. dollar as we expand our international operation and our risk grows. As of December 31, 2018, substantially all of our total liabilities were denominated in the United States dollar.

Inflation generally affects us by increasing our cost of labor. We do not believe that inflation had a material effect on our business, financial condition or results of operations during the year ended December 31, 2018.

Item 8. Financial Statements and Supplementary Data.

Our consolidated financial statements, together with the report of our independent registered public accounting firm, appear on pages F-1 through F-24 of this Annual Report on Form 10-K.

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

There has been no change of accountants nor any disagreements with accountants on any matter of accounting principles or practices or financial disclosure required to be reported under this Item.

Item 9A. Controls and Procedures.

Evaluation of Disclosure Controls and Procedures

The Company has established disclosure controls and procedures (as defined in Rules 13a-15(e) and 15d-15(e) under the Exchange Act) designed to ensure that information required to be disclosed in the reports that the Company files or submits under the Exchange Act is recorded, processed, summarized and reported within the time periods specified in the SEC's rules and forms and is accumulated and communicated to management, including the principal executive officer (our Chief Executive Officer) and principal financial officer (our Vice President, Finance), to allow timely decisions regarding required disclosure.

The Company's management, with the participation of the Company's Chief Executive Officer and Vice President, Finance, evaluated the effectiveness of the Company's disclosure controls and procedures (as defined in Rules 13a-15(e) and 15d-15(e) under the Exchange Act) as of December 31, 2018. 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 disclosure controls and procedures have been designed to provide reasonable assurance of achieving their objectives. Based on the evaluation of the Company's disclosure controls and procedures as of December 31, 2018, the Company's Chief Executive Officer and Vice President, Finance concluded that, as of such date, the Company's disclosure controls and procedures were effective at the reasonable assurance level.

Management's Annual Report on Internal Control Over Financial Reporting

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

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

Because of its inherent limitations, internal control over financial reporting may not prevent or detect misstatements. Therefore, even those systems determined to be effective can provide only reasonable assurance with respect to financial statement preparation and presentation. Projections of any evaluation of effectiveness to future periods are subject to the risk that controls may become inadequate because of changes in conditions, or that the degree of compliance with the policies or procedures may deteriorate.

Our management assessed the effectiveness of our internal control over financial reporting as of December 31, 2018. In making this assessment, management used the criteria set forth by the Committee of Sponsoring Organizations of the Treadway Commission in *Internal Control—Integrated Framework* (2013 framework) (COSO). Based on its assessment, management believes that, as of December 31, 2018, our internal control over financial reporting is effective based on those criteria.

Changes in Internal Control over Financial Reporting

There was no other change in our internal control over financial reporting that occurred during the fiscal quarter ended December 31, 2018 that has materially affected, or is reasonably likely to materially affect, our internal control over financial reporting.

Item 9B. Other Information.

None.

PART III

Item 10. Directors, Executive Officers and Corporate Governance.

The information required by this item regarding directors, executive officers and corporate governance will be included in our 2019 Proxy Statement, which we intend to file with the Securities and Exchange Commission within 120 days of the end of our fiscal year pursuant to General Instruction G(3) of Form 10-K, and is incorporated herein by reference.

Item 11. Executive Compensation.

The information required by this item regarding executive compensation will be included in our 2019 Proxy Statement, which we intend to file with the Securities and Exchange Commission within 120 days of the end of our fiscal year pursuant to General Instruction G(3) of Form 10-K, and is incorporated herein by reference.

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

The information required by this item regarding security ownership of certain beneficial owners and management and securities authorized for issuance under equity compensation plans will be included in our 2019 Proxy Statement, which we intend to file with the Securities and Exchange Commission within 120 days of the end of our fiscal year pursuant to General Instruction G(3) of Form 10-K, and is incorporated herein by reference.

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

The information required by this item regarding certain relationships and related transactions and director independence will be included in our 2019 Proxy Statement, which we intend to file with the Securities and Exchange Commission within 120 days of the end of our fiscal year pursuant to General Instruction G(3) of Form 10-K, and is incorporated herein by reference.

Item 14. Principal Accountant Fees and Services.

The information required by this item regarding principal accounting fees and services will be included in our 2019 Proxy Statement, which we intend to file with the Securities and Exchange Commission within 120 days of the end of our fiscal year pursuant to General Instruction G(3) of Form 10-K, and is incorporated herein by reference.

INDEX TO CONSOLIDATED FINANCIAL STATEMENTS

Report of Independent Registered Public Accounting Firm

To the Stockholders and the Board of Directors
resTORbio, Inc.:

Opinion on the Consolidated Financial Statements

We have audited the accompanying consolidated balance sheets of resTORbio, Inc. and its subsidiary (the Company) as of December 31, 2018 and 2017, the related consolidated statements of operations and comprehensive loss, redeemable convertible preferred stock and stockholders' equity (deficit), and cash flows for the years ended December 31, 2018 and 2017 and the period July 5, 2016 (inception) through December 31, 2016 and the related notes (collectively, the consolidated financial statements). In our opinion, the consolidated financial statements present fairly, in all material respects, the financial position of the Company as of December 31, 2018 and 2017, and the results of its operations and its cash flows for the years ended December 31, 2018 and 2017 and the period July 5, 2016 (inception) through December 31, 2016 in conformity with U.S. generally accepted accounting principles.

Basis for Opinion

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

We conducted our audits in accordance with the standards of the PCAOB. Those standards require that we plan and perform the audit to obtain reasonable assurance about whether the consolidated financial statements are free of material misstatement, whether due to error or fraud. 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.

Cambridge, Massachusetts
March 18, 2019

resTORbio, Inc.
Consolidated Balance Sheets
(In thousands, except share and per share data)

	December 31, 2018	December 31, 2017
Assets		
Current assets:		
Cash and cash equivalents	$ 7,042	$ 53,349
Marketable securities	100,986	—
Prepaid expenses	1,491	792
Deferred offering costs	—	929
Other current assets	15	84
Total current assets	109,534	55,154
Restricted cash	84	—
Property and equipment, net	321	39
Total assets	$ 109,939	$ 55,193
Liabilities, redeemable convertible preferred stock and stockholders' equity (deficit)		
Current liabilities:		
Accounts payable (including related party amounts of $0 and $32 as of December 31, 2018 and 2017, respectively)	$ 2,989	$ 1,515
Accrued liabilities	2,727	3,987
Total current liabilities	5,716	5,502
Other liabilities	19	—
Total liabilities	5,735	5,502
Commitments and contingencies (see Note 12)		
Redeemable convertible preferred stock:		
Redeemable convertible preferred stock, Series A, $0.0001 par value, no and 15,527,951 shares authorized as of December 31, 2018 and 2017, respectively; no and 15,527,951 shares issued and outstanding as of December 31, 2018 and 2017, respectively; aggregate liquidation preference of $0 and $30,000 as of December 31, 2018 and 2017, respectively	—	41,674
Redeemable convertible preferred stock, Series B, $0.0001 par value, no and 4,792,716 shares authorized as of December 31, 2018 and 2017, respectively; no and 4,792,716 shares issued and outstanding as of December 31, 2018 and 2017, respectively; aggregate liquidation preference of $0 and $40,000 as of December 31, 2018 and 2017, respectively	—	39,946
Stockholders' equity (deficit):		
Preferred stock, $0.0001 par value, 10,000,000 and no shares authorized as of December 31, 2018 and 2017, respectively; no shares issued and outstanding as of December 31, 2018 and 2017	—	—
Common stock, $0.0001 par value, 150,000,000 and 30,000,000 shares authorized as of December 31, 2018 and 2017, respectively; 28,055,344 and 5,659,089 shares issued and outstanding as of December 31, 2018 and 2017, respectively; 28,054,344 and 4,562,640 shares vested as of December 31, 2018 and 2017, respectively	3	1
Additional paid-in capital	175,635	1,849
Accumulated deficit	(71,393)	(33,779)
Other comprehensive loss	(41)	—
Total stockholders' equity (deficit)	104,204	(31,929)
Total liabilities, redeemable convertible preferred stock and stockholders' equity (deficit)	$ 109,939	$ 55,193

See accompanying notes to these consolidated financial statements.

resTORbio, Inc.
Consolidated Statements of Operations and Comprehensive Loss
(In thousands, except share and per share data)

	Year Ended December 31, 2018	Year Ended December 31, 2017	July 5, 2016 (inception) through December 31, 2016
Operating expenses:			
Research and development	$ 31,065	$ 16,839	$ —
General and administrative	8,640	2,043	1
Total operating expenses	39,705	18,882	1
Loss from operations	(39,705)	(18,882)	(1)
Other Income, net	2,117	(14,896)	—
Loss before income taxes	(37,588)	(33,778)	(1)
Income tax expense	26	—	—
Net loss	$ (37,614)	$ (33,778)	$ (1)
Net loss per share, basic and diluted	$ (1.42)	$ (8.42)	$ (0.00)
Weighted-average common shares used in computing net loss per share, basic and diluted	26,439,216	4,009,513	1,978,137
Other comprehensive loss:			
Unrealized losses on marketable securities	$ (41)	$ —	$ —
Total other comprehensive loss	(41)	—	—
Comprehensive loss	$ (37,655)	$ (33,778)	$ (1)

See accompanying notes to these consolidated financial statements.

resTORbio, Inc.
Consolidated Statements of Redeemable Convertible Preferred Stock and Stockholders' Equity (Deficit)
(In thousands, except share data)

	Series A Redeemable Convertible Preferred Stock		Series B Redeemable Convertible Preferred Stock		Common Stock		Additional Paid In	Accumulated	Comprehensive	Shareholders' (Deficit)
	Shares	Amount	Shares	Amount	Shares	Amount	Capital	Deficit	Income (Loss)	Equity
Balance at July 5, 2016	—	$ —	—	$ —	—	$ —	$ —	$ —	$ —	$ —
Vesting of restricted shares	—	—	—	—	2,082,860	1	—	—	—	1
Net loss	—	—	—	—	—	—	—	(1)	—	(1)
Balance at December 31, 2016	—	$ —	—	$ —	2,082,860	$ 1	$ —	$ (1)	$ —	$ —
Issuance of common shares to PureTech (see Note 14)	—	—	—	—	1,886,363	—	—	—	—	—
Issuance of Series A redeemable convertible preferred stock, net of tranche liability	15,527,951	41,674	—	—	—	—	1,379	—	—	1,379
Issuance of Series B redeemable convertible preferred stock, net of issuance costs of $54	—	—	4,792,716	39,946	—	—	—	—	—	—
Vesting of restricted shares	—	—	—	—	593,417	—	—	—	—	—
Stock-based compensation expense	—	—	—	—	—	—	470	—	—	470
Net loss	—	—	—	—	—	—	—	(33,778)	—	(33,778)
Balance at December 31, 2017	15,527,951	$ 41,674	4,792,716	$ 39,946	4,562,640	$ 1	$ 1,849	$ (33,779)	$ —	$ (31,929)
Conversion of convertible preferred stock into common stock upon the closing of initial public offering	(15,527,951)	(41,674)	(4,792,716)	(39,946)	15,870,559	1	81,619	—	—	81,620
Issuance of common stock upon closing of initial public offering, net of issuance costs of $8,379	—	—	—	—	6,516,667	1	89,369	—	—	89,370
Vesting of restricted shares	—	—	—	—	1,097,449	—	865	—	—	865
Exercise of stock options	—	—	—	—	7,029	—	5	—	—	5
Stock-based compensation expense	—	—	—	—	—	—	1,928	—	—	1,928
Net loss	—	—	—	—	—	—	—	(37,614)	—	(37,614)
Unrealized losses on marketable securities	—	—	—	—	—	—	—	—	(41)	(41)
Balance at December 31, 2018	—	$ —	—	$ —	28,054,344	$ 3	$ 175,635	$ (71,393)	$ (41)	$ 104,204

See accompanying notes to these consolidated financial statements.

resTORbio, Inc.
Consolidated Statements of Cash Flows
(In thousands)

	Year Ended December 31, 2018	Year Ended December 31, 2017	July 5, 2016 (inception) through December 31, 2016
Operating activities:			
Net loss	$ (37,614)	$ (33,778)	$ (1)
Adjustments to reconcile net loss to net cash used in operating activities:			
Accretion on marketable securities	(673)	—	—
Depreciation and amortization expense	80	5	—
Stock-based compensation expense	2,793	470	—
Change in fair value of tranche liability	—	14,896	—
Expense related to acquisition of intellectual property (see Note 6)	—	3,157	—
Changes in operating assets and liabilities:			
Restricted cash	(84)	—	—
Prepaid expenses and other current assets	(630)	(876)	—
Accounts payable	1,597	1,392	—
Accrued liabilities	(1,022)	3,749	1
Other liabilities	19	—	—
Net cash used in operating activities	(35,534)	(10,985)	—
Investing activities:			
Purchases of property and equipment	(362)	(44)	—
Maturities of marketable securities	7,500	—	—
Purchase of marketable securities	(107,854)	—	—
Net cash used in investing activities	(100,716)	(44)	—
Financing activities:			
Proceeds from issuance of Series A redeemable convertible preferred stock	—	25,000	—
Proceeds from issuance of Series B redeemable convertible preferred stock, net	—	39,946	—
Proceeds from initial public offering, net of issuance costs	90,908	—	—
Deferred offering costs	(970)	(568)	—
Proceeds from exercise of stock options	5	—	—
Net cash provided by financing activities	89,943	64,378	—
Net (decrease) increase in cash and cash equivalents	(46,307)	53,349	—
Cash and cash equivalents at beginning of period	53,349	—	—
Cash and cash equivalents at end of period	$ 7,042	$ 53,349	$ —
Supplemental disclosure of non-cash investing and financing activities:			
Conversion of redeemable convertible preferred stock into common stock	$ 81,620	$ —	$ —

See accompanying notes to these consolidated financial statements.

1. Organization

resTORbio, Inc. ("the Company") was incorporated in the State of Delaware on July 5, 2016. The Company is a clinical-stage biopharmaceutical company focused on the development and commercialization of novel therapeutics for the treatment of aging-related diseases and conditions. The Company's principal operations are located in Boston, Massachusetts.

Since inception, the Company has been primarily involved in research and development activities. The Company devotes substantially all of its efforts to product research and development, initial market development and raising capital. The Company has not generated any product revenue related to its primary business purpose to date and is subject to a number of risks similar to those of other early stage companies, including dependence on key individuals, competition from other companies, the need for development of commercially viable products and the need to obtain adequate additional financing to fund the development of its product candidates. The Company is also subject to a number of risks similar to other companies in the life sciences industry, including regulatory approval of products, uncertainty of market acceptance of products, competition from substitute products and larger companies, the need to obtain additional financing, compliance with government regulations, protection of proprietary technology, dependence on third parties, product liability and dependence on key individuals.

Initial Public Offering

On January 30, 2018, the Company completed its initial public offering ("IPO"), whereby the Company sold 6,516,667 shares of its common stock (inclusive of 850,000 shares of common stock sold by the Company pursuant to the full exercise of an overallotment option granted to the underwriters in connection with the offering) at a price of $15.00 per share. The shares began trading on The Nasdaq Global Select Market on January 26, 2018. The aggregate net proceeds received by the Company from the offering were approximately $89.4 million, after deducting underwriting discounts and commissions and other offering expenses payable by the Company. As of December 31, 2017, the Company had incurred $0.9 million of costs related to the IPO which have been deferred. Upon the closing of the IPO, all outstanding shares of redeemable convertible preferred stock converted into 15,870,559 shares of common stock and all unvested shares of restricted stock automatically vested. Additionally, the Company is now authorized to issue 10,000,000 shares of preferred stock and 150,000,000 shares of common stock.

Liquidity

In the course of its development activities, the Company has sustained operating losses and expects such losses to continue over the next several years. The Company's ultimate success depends on the outcome of its research and development activities. The Company has incurred net losses from operations since inception and has an accumulated deficit of $71.4 million as of December 31, 2018. The Company believes that its cash, cash equivalents, and marketable securities will be sufficient to fund the Company's current operating plan through at least the next twelve months.

2. Summary of Significant Accounting Policies

Basis of Presentation and Use of Estimates

The accompanying consolidated financial statements have been prepared in accordance with U.S. generally accepted accounting principles ("U.S. GAAP"). The Company's fiscal year end is December 31st. Any reference in these notes to applicable guidance is meant to refer to the authoritative United States generally accepted accounting principles as found in the Accounting Standards Codification ("ASC") and Accounting Standards Updates ("ASUs") of the Financial Accounting Standards Board ("FASB"). The preparation of financial statements in conformity with U.S. GAAP requires management to make estimates and assumptions that affect the reported amounts of assets and liabilities and the disclosure of contingent assets and liabilities, as of the date of the consolidated financial statements, and the reported amounts of any expenses during the reporting period. On an ongoing basis, management evaluates its estimates, including those related to accrued liabilities, fair value of tranche liabilities, and stock-based compensation expense. Management bases its estimates on historical experience, and on various other market-specific relevant assumptions that management believes to be reasonable, under the circumstances. Actual results may differ from those estimates or assumptions.

The consolidated financial statements include the accounts of resTORbio, Inc. and its wholly owned subsidiary, resTORbio Securities Corp. All inter-company transactions and balances have been eliminated in consolidation.

Marketable securities

The Company classifies marketable securities with remaining maturities when purchased of greater than three months as available-for-sale. Marketable securities with a remaining maturity date greater than one year are classified as non-current. Available-for-sale securities are maintained by investment managers and consist of U.S. treasury securities and U.S. government agency securities. Available-for-sale securities are carried at fair value with the unrealized gains and losses included in other comprehensive income (loss) as a component of stockholders' equity until realized. Any premium or discount arising at purchase is amortized and/or accreted to interest income and/or expensed over the life of the instrument.

If any adjustment to fair value reflects a decline in the value of the investment, the Company considers all available evidence to evaluate the extent to which the decline is "other-than-temporary" and, if so, marks the investment to market through a change to the Company's statement of operations and comprehensive loss.

Restricted Cash

The Company maintains a letter of credit for the benefit of the landlord in connection with the Company's office lease. As of December 31, 2018 and 2017, restricted cash (non-current) related to this letter of credit consisted of $84,000 and $0, respectively.

Fair Value Measurements

Fair value is defined as the price at which an asset could be exchanged in a current transaction between knowledgeable, willing parties. A liability's fair value is defined as the amount that would be paid to transfer the liability to a new obligor, not the amount that would be paid to settle the liability with the creditor. Where available, fair value is based on observable market prices, or parameters derived from such prices. Where observable prices or inputs are not available, valuation models are applied. These valuation techniques involve some level of management estimation and judgment. The degree of management estimation and judgment is dependent on the price transparency for the instruments, or market, and the instruments' complexity. The authoritative accounting guidance describes a fair value hierarchy based on three levels of inputs that may be used to measure fair value, of which the first two are considered observable and the last is considered unobservable. These levels of inputs are as follows:

Level 1—Observable inputs such as unadjusted, quoted prices in active markets for identical assets or liabilities at the measurement date.

Level 2—Inputs (other than quoted prices included in Level 1) are either directly or indirectly observable for the asset or liability. These include quoted prices for similar assets or liabilities in active markets and quoted prices for identical or similar assets or liabilities in markets that are not active.

Level 3—Unobservable inputs that reflect management's best estimate of what market participants would use in pricing the asset or liability at the measurement date. Consideration is given to the risk inherent in the valuation technique and the risk inherent in the inputs to the model.

The following table summarizes assets measured at fair value on a recurring basis at December 31, 2018 (in thousands):

Description	December 31, 2018	Active Markets (Level 1)	Observable Inputs (Level 2)	Unobservable Inputs (Level 3)
Money market funds (included in cash and cash equivalents)	$ 6,804	$ 6,804	$ —	$ —
U.S. treasury securities (included in cash and cash equivalents)	238	238	—	—
U.S. treasury securities (included in marketable securities)	100,986	100,986	—	—
Total	$ 108,028	$ 108,028	$ —	$ —

The following table summarizes assets measured at fair value on a recurring basis at December 31, 2017 (in thousands):

Description	December 31, 2017	Active Markets (Level 1)	Observable Inputs (Level 2)	Unobservable Inputs (Level 3)
Money market funds (included in cash and cash equivalents)	$ 53,349	$ 53,349	$ —	$ —
Total	$ 53,349	$ 53,349	$ —	$ —

To the extent that valuation is based on models or inputs that are less observable or unobservable in the market, the determination of fair value requires more judgment. Accordingly, the degree of judgment exercised by the Company in determining fair value is greatest for instruments categorized in Level 3. A financial instrument's level within the fair value hierarchy is based on the lowest level of any input that is significant to the fair value measurement.

An entity may elect to measure many financial instruments and certain other items at fair value at specified election dates. Subsequent unrealized gains and losses on items for which the fair value option has been elected will be reported in net loss. The Company did not elect to measure any additional financial instruments or other items at fair value.

There have been no changes to the valuation methods utilized by the Company during the years ended December 31, 2018 and 2017 and the period from July 5, 2016 (inception) to December 31, 2016. The Company evaluates transfers between levels at the end of each reporting period. There were no transfers of financial instruments between levels during the years ended December 31, 2018 and 2017 and the period from July 5, 2016 (inception) to December 31, 2016.

Concentration of Credit Risk

Financial instruments that potentially subject the Company to a concentration of credit risk consist of cash, cash equivalents and marketable securities. The Company's cash, cash equivalents and marketable securities are held by financial institutions in the United States. Amounts on deposit may at times exceed federally insured limits. Management believes that the financial institution is financially sound, and accordingly, minimal credit risk exists with respect to the financial institution.

Concentration of Manufacturing Risk

As of December 31, 2018, the Company had manufacturing arrangements with vendors for the supply of materials for use in preclinical and clinical studies. If the Company were to experience any disruptions in either party's ability or willingness to continue to provide manufacturing services, the Company may experience significant delays in its product development timelines and may incur substantial costs to secure alternative sources of manufacturing.

Deferred Offering 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 (deficit) as a reduction of proceeds generated as a result of the offering. Should the planned equity financing be abandoned, the deferred offering costs will be expensed immediately as a charge to operating expenses in the consolidated statements of operations and comprehensive loss. The Company recorded deferred offering costs of $0 and $0.9 million as of December 31, 2018 and 2017, respectively.

Property and Equipment

Property and equipment are stated at cost, less accumulated depreciation. Depreciation is recorded using the straight-line method over the estimated useful lives of the respective assets. Depreciation begins at the time the asset is placed in service. Maintenance and repairs that do not improve or extend the lives of the respective assets are expensed to operations as incurred. Upon sale or retirement of assets, the cost and related accumulated depreciation are removed from the consolidated balance sheets and the resulting gain or loss is reflected in the consolidated statements of operations and comprehensive loss.

The estimated useful lives of property and equipment are as follows:

	Useful Life (in years)
Leasehold improvements	Lesser of useful life or remaining lease term
Machinery and equipment	2-8 years
Furniture and fixtures	3-5 years
Computers	1-5 years
Office equipment	3-5 years
Software	3-5 years

Impairment of Long-Lived Assets

The Company evaluates its long-lived assets, including property and equipment, for impairment whenever events or changes in circumstances indicate that the carrying value of these assets may not be recoverable. Recoverability of these assets is measured by comparison of the carrying amount of each asset to the future undiscounted cash flows the asset is expected to generate over its remaining life. If the asset is considered to be impaired, the amount of any impairment is measured as the difference between the carrying value and the fair value of the impaired asset. The Company has recorded no impairment of any long-lived assets during any of the periods presented.

Accrued Research and Development Costs

The Company accrues for estimated costs of research and development activities conducted by third-party service providers, which include the conduct of preclinical studies and clinical trials, and contract manufacturing activities. The Company records the estimated costs of research and development activities based upon the estimated amount of services provided and includes these costs in accrued liabilities in the consolidated balance sheets and within research and development expenses in the consolidated statements of operations and comprehensive loss. These costs are a significant component of the Company's research and development expenses. The Company accrues for these costs based on factors such as estimates of the work completed and in accordance with agreements established with its third-party service providers. The Company estimates the amount of work completed by its third-party service providers through discussions with internal personnel and external service providers as to the progress or stage of completion of the services and the agreed-upon fee to be paid for such services. The majority of the Company's service providers invoice in arrears for services performed, on a pre-determined schedule or when contractual milestones are met; however, some require advance payments. The Company makes significant judgments and estimates in determining the accrued balance in each reporting period based on the facts and circumstances known at that time. As actual costs become known, the Company adjusts its accrued estimates. Although the Company does not expect its estimates to be materially different from amounts actually incurred, our understanding of the status and timing of services performed, the number of patients enrolled, and the rate of patient enrollment may vary from its estimates and could result in us reporting amounts that are too high or too low in any particular period. The Company's accrued expenses are dependent, in part, upon the receipt of timely and accurate reporting from clinical research organizations, or CROs, clinical manufacturing organizations, or CMOs, and other third-party service providers. To date, there have been no material differences from its accrued expenses to actual expenses.

Research and Development Costs

Research and development costs are expensed as incurred and consist of personnel costs, lab supplies and other costs, as well as fees paid to third parties to conduct research and development activities on the Company's behalf. Amounts incurred in connection with license agreements are also included in research and development expenses. The Company records payments made to outside vendors for services performed or goods being delivered for use in research and development activities as either prepaid expenses or accrued expenses, depending on the timing of when services are performed or goods are delivered.

Equity-Based Compensation Expense

The Company recognizes equity-based compensation expense for awards of equity instruments to employees and non-employees based on the grant date fair value of those awards in accordance with FASB ASC Topic 718, *Stock Compensation* ("ASC 718"). ASC 718 requires all equity-based compensation awards to employees and non-employee directors, including grants of restricted shares and stock options, to be recognized as expense in the consolidated statements of operations and comprehensive loss based on their grant date fair values. The Company estimates the fair value of stock options using the Black-Scholes option pricing model. The Company uses the value of its common stock to determine the fair value of restricted shares.

The Company accounts for restricted stock and common stock options issued to non-employees under FASB ASC Topic 505-50, *Equity- Based Payments to Non-Employees* ("ASC 505-50"). As such, the value of such options is periodically remeasured and income or expense is recognized over their vesting terms. Compensation cost related to awards with service-based vesting schedules is recognized using the straight-line method. The Company determines the fair value of the restricted stock and common stock granted to non-employees as either the fair value of the consideration received or the fair value of the equity instruments issued.

The Black-Scholes option pricing model requires the input of certain subjective assumptions, including (i) the expected share price volatility, (ii) the expected term of the award, (iii) the risk-free interest rate and (iv) the expected dividend yield. Due to the lack of a public market for the trading of the Company's common stock and a lack of company-specific historical and implied volatility data, the Company has based its estimate of expected volatility on the historical volatility of a group of similar companies that are publicly traded. The historical volatility is calculated based on a period of time commensurate with the expected term assumption. The group of representative companies have characteristics similar to the Company, including stage of product development and focus on the life science industry. The Company uses the simplified method, which is the average of the final vesting tranche date and the contractual term, to calculate the expected term for options granted to employees as it does not have sufficient historical exercise data to provide a reasonable basis upon which to estimate the expected term. For options granted to non-employees, the Company utilizes the contractual term of the arrangement as the basis for the expected term assumption. The risk-free interest rate is based on a treasury instrument whose term is consistent with the expected term of the stock options. The Company uses an assumed dividend yield of zero as the Company has never paid dividends and has no current plans to pay any dividends on its common stock.

The Company expenses the fair value of its equity-based compensation awards granted to employees on a straight-line basis over the associated service period, which is generally the period in which the related services are received. The Company measures equity-based compensation awards granted to non-employees at fair value as the awards vest and recognizes the resulting value as compensation expense at each financial reporting period. The Company accounts for award forfeitures as they occur.

Determination of Fair Value of Common and Preferred Shares and Tranche Rights Liability

Prior to the completion of the Company's IPO, the Company was required to estimate the fair value of its common stock underlying its stock-based awards when performing the fair value calculations using the Black-Scholes option pricing model. The estimated fair value of the Company's common and preferred shares has been determined by the board of directors as of the grant date, with input from management, considering the Company's most recently available third-party valuations of common shares and the board of directors' assessment of additional objective and subjective factors that it believed were relevant and which may have changed from the date of the most recent third-party valuation through the date of the grant. These third-party valuations were performed in accordance with the guidance outlined in the American Institute of Certified Public Accountants' Accounting and Valuation Guide, *Valuation of Privately-Held-Company Equity Securities Issued as Compensation*. The Company's common and preferred share valuations were prepared using either an option-pricing method, or OPM, or a probability-weighted expected return method, or PWERM, which uses a combination of market approaches and an income approach to estimate the Company's enterprise value. The OPM treats common securities and preferred securities as call options on the total equity value of a company, with exercise prices based on the value thresholds at which the allocation among the various holders of a company's securities changes. Under this method, the common and preferred shares have value only if the funds available for distribution to members are expected to exceed the value of the preferred security liquidation preference at the time of the liquidity event, such as a strategic sale or a merger. The PWERM is a scenario-based methodology that estimates the fair value of common and preferred shares based upon an analysis of future values for the enterprise, assuming various outcomes. The common and preferred share values are based on the probability-weighted present value of expected future investment returns considering each of the possible outcomes available as well as the rights of each class of common and preferred securities. The future value of the common and preferred shares under each outcome is discounted back to the valuation date at an appropriate risk-adjusted discount rate and probability weighted to arrive at an indication of value for the common and preferred shares. The estimated fair value of the Tranche Rights was determined using the difference between the total purchase price of the Company's preferred stock and the total fair value of the preferred stock using a risk-adjusted forward contract model.

Income Taxes

The Company uses the asset and liability method of accounting for income taxes in accordance with FASB ASC Topic 740, *Income Taxes*. Under this method, deferred tax assets and liabilities are determined based on the differences between the financial reporting and the tax basis of assets and liabilities, and are measured using the enacted tax rates and laws that will be in effect when the differences are expected to reverse. The Company must then assess the likelihood that the resulting deferred tax assets will be realized. A valuation allowance is provided when it is more likely than not that some portion, or all of a deferred tax asset will not be realized. Due to the Company's lack of earnings history, the net deferred tax assets have been fully offset by a valuation allowance.

The Company recognizes benefits of uncertain tax positions if it is more likely than not that such positions will be sustained upon examination based solely on their technical merits, as the largest amount of benefit that is more likely than not to be realized upon the ultimate settlement. The Company's policy is to recognize interest and penalties related to the underpayment of income taxes as a component of income tax expense or benefit. To date, the Company has no uncertain tax positions and there have been no interest charges or penalties related to unrecognized tax benefits.

Net Loss per Share

Basic net loss per share is calculated by dividing the net loss by the weighted average number of shares of common stock outstanding during the period without consideration of common stock equivalents. Diluted net loss per common share is the same as basic net loss per common share for all periods presented, since the effects of potentially dilutive securities are antidilutive.

Recently Adopted Accounting Pronouncements

In May 2017, the FASB issued ASU 2017-09, *Compensation—Stock Compensation* (Topic 718): Scope of Modification Accounting ("ASU 2017-09"). ASU 2017-09 provides guidance about which changes to the terms or conditions of a share-based payment award require an entity to apply modification accounting in Topic 718. The guidance is effective for annual periods beginning after December 15, 2017, with early adoption permitted, including adoption in any interim period for which financial statements have not yet been issued. The Company adopted the provisions of ASU 2017-09 on January 1, 2018. No modifications of share-based payment awards have occurred as of December 31, 2018.

Recently Issued Accounting Pronouncements

In February 2016, the FASB issued ASU 2016-02, *Leases* ("ASU 2016-02"), which requires a lessee to recognize a right-of-use asset and a lease liability for operating leases, initially measured at the present value of the future lease payments, in the balance sheet. ASU 2016-02 also requires a lessee to recognize a single lease cost, calculated so that the cost of the lease is allocated over the lease term, generally on a straight-line basis. This new guidance is effective for fiscal years beginning after December 15, 2019. Early adoption is permitted. The Company is currently evaluating the potential effects of adopting the provisions of ASU 2016-02 on its consolidated financial statements.

In November 2016, the FASB issued ASU 2016-18, *Statement of Cash Flows* ("ASU 2016-18"), which requires that amounts generally described as restricted cash and restricted cash equivalents should be included with cash and cash equivalents when reconciling the beginning-of-period and end-of-period total amounts shown on the statement of cash flows. ASU 2016-18 is effective for fiscal years beginning after December 15, 2018 and interim periods in fiscal years beginning after December 15, 2019 and should be applied using a retrospective transition method to each period presented. Early adoption is permitted. The Company does not expect the impact of ASU 2016-18 to be material to its consolidated financial statements.

In July 2017, the FASB issued ASU 2017-11, *Accounting for Certain Financial Instruments with Down Round Features* ("ASU 2017-11"), which updates the guidance related to the classification analysis of certain equity-linked financial instruments (or embedded features) with down round features. Under ASU 2017-11, a down round feature no longer precludes equity classification when assessing whether the instrument is indexed to an entity's own stock. As a result, a freestanding equity-linked financial instrument (or embedded conversion option) no longer would be accounted for as a derivative liability at fair value as a result of the existence of a down round feature. For freestanding equity classified financial instruments, the amendments require entities that present earnings per share ("EPS") in accordance with Topic 260 to recognize the effect of the down round feature when it is triggered. That effect is treated as a dividend and as a reduction of income available to common shareholders in basic EPS. ASU 2017-11 is effective for public entities for all annual and interim periods beginning after December 15, 2019. Early adoption is permitted. The Company does not expect the impact of ASU 2017-11 to be material to its consolidated financial statements.

In June 2018, the FASB issued ASU No. 2018-07, *Compensation – Stock Compensation (Topic 718), Improvements to Nonemployee Share-Based Payment Accounting* ("ASU 2018-07"), which intends to simplify aspects of share-based compensation issued to non-employees by making the guidance consistent with the accounting for employee share-based compensation. For public entities, ASU 2018-07 is required to be adopted for annual periods beginning after December 15, 2018, including interim periods within those fiscal years. For non-public entities and emerging growth companies that choose to take advantage of the extended transition period, ASU 2018-07 is effective for annual periods beginning after December 15, 2019. Early adoption is permitted for all entities but no earlier than the Company's adoption of ASC 606. The Company is currently evaluating the impact that the adoption of ASU 2018-07 will have on its financial statements.

3. Marketable Securities

As of December 31, 2018, the fair value of marketable securities by type of security was as follows (in thousands):

Description	Amortized Cost	Unrealized Gains	Unrealized Losses	Fair Value
U.S. government agency treasuries and securities	$ 101,027	$ —	$ 41	$ 100,986
Total	$ 101,027	$ —	$ 41	$ 100,986

The Company did not have any marketable securities as of December 31, 2017.

The estimated fair value and amortized cost of the Company's available-for-sale securities by contractual maturity are summarized as follows (in thousands):

	December 31, 2018	
	Amortized Cost	Fair Value
Due in one year or less	$ 101,027	$ 100,986
Total	$ 101,027	$ 100,986

4. Property and Equipment, Net

Property and equipment, net consists of the following:

	As of December 31,	
	2018	2017
	(In thousands)	
Leasehold improvements	$ 65	$ —
Machinery and equipment	38	38
Furniture and fixtures	194	—
Computers	76	6
Office equipment	11	—
Software	22	—
Total property and equipment	406	44
Less: accumulated depreciation	(85)	(5)
Property and equipment, net	$ 321	$ 39

Depreciation expense was $80,000, $5,000, and $0 for the years ended December 31, 2018 and 2017 and the period from July 5, 2016 (inception) to December 31, 2016, respectively.

5. Accrued Liabilities

Accrued liabilities consist of the following:

	As of December 31,	
	2018	2017
	(In thousands)	
Accrued payroll and related expenses	$ 1,189	$ 394
Accrued research and development expenses	1,028	3,250
Deferred offering costs	—	238
Other	510	105
Total accrued liabilities	$ 2,727	$ 3,987

6. License Agreements

Novartis License Agreement

On March 23, 2017, the Company entered into an exclusive license agreement with Novartis International Pharmaceutical Ltd. (“Novartis”). Under the agreement, Novartis granted the Company an exclusive, field-restricted, worldwide license, to certain intellectual property rights owned or controlled by Novartis, to develop, commercialize and sell one or more therapeutic products comprising RTB101 or RTB101 in combination with everolimus in a fixed dose combination. The exclusive field under the license agreement is for the treatment, prevention and diagnosis of disease and other conditions in all indications in humans and animals.

As initial consideration for the licensed rights, the Company issued Novartis Institutes for Biomedical Research (“NIBR”) 2,587,992 shares of the Company’s Series A Preferred Stock. The fair value of the Novartis license was $3.2 million based on the fair value of the Series A Preferred Stock which was determined to be $1.22 per share based on an independent third-party valuation, and is recorded as research and development expenses in the consolidated statements of operations and comprehensive loss.

The agreement may be terminated by either party upon a material breach by the other party that is not cured within 60 days after written notice. The Company may terminate the agreement in its entirety or on a product-by-product or country-by-country basis with or without cause with 60 days’ prior written notice.

Novartis may terminate the portion of the agreement related to everolimus if the Company fails to use commercially reasonable efforts to research, develop and commercialize a product utilizing everolimus for a period of three years. Novartis may terminate the license agreement upon the Company’s bankruptcy, insolvency, dissolution or winding up.

As additional consideration for the license, the Company is required to pay up to an aggregate of $4.3 million upon the satisfaction of clinical milestones, up to an aggregate of $24 million upon the satisfaction of regulatory milestones for the first indication approved, and up to an aggregate of $18 million upon the satisfaction of regulatory milestones for the second indication approved. In addition, the Company is required to pay up to an aggregate of $125 million upon the satisfaction of commercial milestones, based on the amount of annual net sales. The Company is also required to pay tiered royalties ranging from a mid single-digit percentage to a low teen-digit percentage on annual net sales of products. These royalty obligations last on a product-by-product and country-by-country basis until the latest of (i) the expiration of the last valid claim of a Novartis patent covering a subject product, (ii) the expiration of any regulatory exclusivity for the subject product in a country, or (iii) the 10th anniversary of the first commercial sale in the country, and are subject to a reduction after the expiration of the last valid claim of a Novartis patent or the introduction of a generic equivalent of a product in a country.

Milestone payments to Novartis will be recorded as research and development expenses in the consolidated statements of operations and comprehensive loss once achievement of each associated milestone has occurred or the achievement is considered probable. In May 2017, the Company initiated a Phase 2b clinical trial for a first indication, triggering the first milestone payment under the agreement. Accordingly, the Company paid the related $0.3 million payment in May 2017. As of December 31, 2018, none of the remaining development milestones, regulatory milestones, sales milestones, or royalties had been reached or were probable of achievement.

7. Research Funding Agreement

On March 6, 2018, the Company and the Silverstein Foundation for Parkinson's with GBA (the "Silverstein Foundation") entered into a research funding agreement (the "Funding Agreement"). One of the Company's directors is a co-founder and current trustee of the Silverstein Foundation. Under the terms of the Funding Agreement, the Silverstein Foundation will partially fund the preclinical research, development work, and Phase 2 clinical trial expenses (the "Research") to be conducted and borne by the Company in connection with the development of RTB101, alone or in combination with other products (the "Product").

Upon execution of the Funding Agreement, the Silverstein Foundation paid the Company an upfront sum of $0.5 million (the "Funding Amount"). The Company is entitled to use the Funding Amount solely to conduct the Research and is obligated to repay the Funding Amount in full to the Silverstein Foundation if it successfully conducts a positive Phase 3 clinical trial of the Product for Parkinson's Disease. The Company is solely responsible for commencing and conducting the Research and will furnish periodic progress updates to the Silverstein Foundation throughout the term of the Funding Agreement. After completing the Research, the Company must provide the Silverstein Foundation with a formal report describing the work performed and the results of the Research.

The Company recognizes proceeds received from the Silverstein Foundation as a reduction to research and development expenses, rather than as revenue, in the consolidated statements of operations and comprehensive loss because the corresponding Funding Agreement does not contain specified performance obligations other than to conduct research on a particular program or in a particular field and no obligations to deliver specified products or technology.

For funds received under the Funding Agreement, the Company recognizes a reduction in research and development expenses in an amount equal to the qualifying expenses incurred in each period up to the amount funded by the Silverstein Foundation. Funding that has been received by the Company in advance of incurring qualifying expenses is recorded in the consolidated balance sheet as funding advance. As of December 31, 2018, $0.5 million qualifying expenses have been incurred. Therefore, all amounts received have been recorded as a reduction of the research and development expense.

8. Preferred Stock and Redeemable Convertible Preferred Stock

As of December 31, 2018, the Company had 10,000,000 shares of preferred stock authorized and none issued and outstanding. As of December 31, 2017, the Company had 20,320,667 shares of preferred stock authorized, of which 15,527,951 shares were issued and outstanding and were designated as $0.0001 par value Series A Preferred Stock and 4,792,716 shares were issued and outstanding and were designated as $0.0001 par value Series B Preferred Stock.

Upon completion of the Company's initial public offering in January 2018, all the outstanding preferred stocks of the Company automatically converted into 15,870,559 shares of the Company's common stock. As of December 31, 2018, no shares of preferred stock were outstanding.

The Company's redeemable convertible preferred shares were classified as temporary or mezzanine equity on the accompanying consolidated balance sheets in accordance with U.S. GAAP for the classification and measurement of redeemable securities as the Series A and Series B Preferred Stock were contingently redeemable at the option of the holder for reasons outside of the Company's control. As of December 31, 2017, there were no accretion of the redeemable convertible preferred shares to redemption value as at that date the shares were not redeemable or probable of being redeemed.

On March 23, 2017, the Company entered into a Series A Preferred Stock Purchase Agreement with PureTech Health LLC ("PureTech") and NIBR. Under the agreement, in the initial March 2017 closing, PureTech purchased 2,846,791 shares of Series A Preferred Stock at a purchase price of $1.932 per share, resulting in aggregate gross proceeds of $5.5 million, and NIBR was issued 2,587,992 shares of Series A Preferred Stock as consideration for an exclusive, field-restricted, worldwide license, to certain intellectual property rights owned or controlled by Novartis, to develop, commercialize and sell one or more therapeutic products comprising RTB101, alone or in combination with everolimus in a fixed dose combination (See Note 6). PureTech also agreed to purchase up to 4,917,185 additional shares, for total aggregate gross proceeds of $9.5 million (the "Tranche Rights"), at $1.932 per share at separate second and third closings to take place upon the occurrence of certain events as specified under the agreement. The fair value of the Series A Preferred Stock on the date of issuance was determined to be $1.22 per share based on an independent third-party valuation.

On March 23, 2017, the Company also entered into a side letter with PureTech under which PureTech agreed to purchase up to 5,175,984 additional shares at $1.932 per share at a fourth closing to take place on a future date based on the occurrence of certain events as specified under the letter. The Series A Tranche Rights were evaluated under ASC 480 – *Distinguishing Liabilities from Equity* and it was determined that they met the requirements for separate accounting from the initial issuance of Series A Preferred Stock as freestanding financial instruments and are accounted for as liabilities. The Company adjusted the carrying value of the Series A Tranche Rights to its estimated fair value at each reporting date up to the closing of each tranche financing. Increases or decreases in fair value of the Tranche Rights were recorded as other income (expense) in the consolidated statements of operations and comprehensive loss.

At the date of issuance, $2.0 million of the Series A Preferred Stock proceeds was allocated to the Series A Tranche Rights liability, which was recorded as a current liability on the consolidated balance sheets.

In September 2017, under the Series A Tranche Rights, the Company received gross proceeds of $4.5 million in exchange for the issuance of 2,329,193 shares of Series A Preferred Stock at $1.932 per share pursuant to the second closing on August 29, 2017. The fair value of the Series A Preferred Stock on the date of issuance was determined to be $1.34 per share based on an independent third-party valuation and the fair value of the Series A Tranche Rights liability was revalued to its estimated fair value of $1.4 million, resulting in other income of $0.6 million.

On October 12, 2017, the Company amended the Series A Preferred Stock Purchase Agreement to accelerate the third and fourth closings under the original agreement. The Company issued 7,763,975 shares of Series A Preferred Stock at $1.932 per share for aggregate gross proceeds of $15.0 million, of which $9.0 million was from PureTech and $6.0 million from a new investor. The fair value of the Series A Preferred Stock on the date of issuance was determined to be $4.11 per share based on an independent third-party valuation and the fair value of the Series A Tranche Rights liability was revalued to its estimated fair value of $10.1 million, resulting in other expense of $8.8 million. Following this closing of the Series A Preferred Stock financing, the Series A Tranche Rights were terminated.

In connection with the October 12, 2017 Series A closing, a new investor entered into a commitment to purchase up to $20 million dollars of Series B Preferred Stock at a purchase price of $8.346 (the "Series B Tranche Right"). The new investor's commitment to purchase Series B Preferred Stock was also determined to meet the requirements for separate accounting. The Series B Tranche Right was determined to be a freestanding financial instrument accounted for as an asset. On October 12, 2017, $6.8 million of the Series A Preferred Stock proceeds were allocated to this liability.

On October 27, 2017, the Company entered into the Series B Preferred Stock Agreement for the issuance and sale of up to 4,792,716 shares of Series B Preferred Stock at $8.346 per share. On November 29, 2017, the Company issued and sold 4,792,716 shares of Series B Preferred Stock at $8.346 per share for aggregate gross proceeds of $40.0 million (the "Series B Financing"), of which $20.0 million satisfied the series B Tranche Right.

The Company measured the fair value of the Tranche Rights liabilities/assets from issuance on March 23, 2017 to settlement on November 29, 2017. The Tranche Rights liabilities/assets are considered a Level 3 liability/asset because its fair value measurement is based, in part, on significant inputs not observed in the market. Any reasonable changes in the assumptions used in the valuation could materially affect the financial results of the Company.

The following is a summary of the changes in fair value of the Tranche Rights and the impact on the consolidated financial statements:

	(In thousands)	Financial statement impacted
Beginning Balance, January 1, 2017	$ —	
Establishment of Series A tranche right liability on March 23, 2017	2,014	Consolidated balance sheets
Change in fair value of Series A tranche right liability immediately prior to second closing on September 8, 2017	(605)	Consolidated statements of operations and comprehensive loss
Mark-to-market of Series A tranche rights liability at September 30, 2017	(30)	Consolidated statements of operations and comprehensive loss
Change in fair value of tranche right liability immediately prior to final closing of the Series A on October 12, 2017	8,767	Consolidated statements of operations and comprehensive loss
Settlement of Series A tranche right liability upon closing of Series A on October 12, 2017	(10,146)	Consolidated balance sheets
Establishment of Series B tranche right asset on October 23, 2017	6,764	Consolidated statements of operations and comprehensive loss
Settlement of Series B tranche right asset upon closing of Series B on November 29, 2017	(6,764)	Consolidated balance sheets
Ending Balance, December 31, 2017	$ —	

The change in the fair value of the Tranche Rights is influenced primarily by the price of the underlying Series A and Series B Preferred Stock. The net change in fair value of $14.9 million for the year ended December 31, 2017 was recorded as other expense in the accompanying consolidated statements of operations and comprehensive loss.

9. Common Stock

General

The voting, dividend and liquidation rights of the holders of common stock are subject to and qualified by the rights, powers, and preferences of the holders of the shares of preferred stock. The common stock has the following characteristics:

Voting

The holders of the common stock are entitled to one vote for each share of common stock held at all meetings of stockholders and written actions in lieu of meetings, provided, however, that except as otherwise required by law, holders of common stock as such shall not be entitled to vote on any amendment to the Company's Certificate of Incorporation that relates solely to the terms of one or more outstanding series of Preferred Stock if the holders of such affected series are entitled, either separately or together with the holders of one or more other such series, to vote thereon pursuant to the Company's Certificate of Incorporation or pursuant to Delaware General Corporation Law. There shall be no cumulative voting.

Dividends

The holders of shares of common stock are entitled to receive dividends, if and when declared by the Board of Directors. Cash dividends may not be declared or paid to the holders of common stock until paid on the preferred stock. As of December 31, 2018, no dividends have been declared or paid since the Company's inception.

Liquidation

After payment to the holders of shares of preferred stock of their liquidation preference, the holders of the common stock are entitled to share ratably in the Company's assets available for distribution to stockholders, in the event of any voluntary or involuntary liquidation, dissolution or winding up of the Company or upon the occurrence of a Deemed Liquidation Event.

Reserve for future issuance

As of December 31, 2016, the Company had not reserved any shares of common stock for future issuance. As of December 31, 2018 and 2017, the Company has reserved the following number of shares of common stock for future issuance upon the conversion of preferred stock, exercise of options or grant of equity awards:

	As of December 31,	
	2018	2017
Redeemable convertible preferred stock, on an as-converted basis	—	15,870,559
Options issued and outstanding	1,122,677	195,668
Unvested restricted stock units	24,960	—
Options available for future grants	1,350,582	1,670,341
Shares available for issuance under the 2018 ESPP	275,030	—
Total	2,773,249	17,736,568

10. Stock-based Compensation

In 2017, the Company adopted the 2017 Stock Incentive Plan (the "Plan"). Under the Plan, shares of the Company's common stock have been reserved for the issuance of stock options to employees, directors, and consultants under terms and provisions established by the Board of Directors. A total of 537,914 shares were reserved for issuance under the Plan. Under the terms of the Plan, options may be granted at an exercise price not less than fair market value. The terms of options granted under the Plan may not exceed ten years. The Board shall determine the terms and conditions of a Restricted Stock Award, including the conditions for vesting and repurchase (or forfeiture) and the issue price, if any. On October 11, 2017, the Company increased the number of shares of common stock available for issuance under the Plan from 537,914 shares to 630,662 shares. On November 29, 2017, the Company increased the number of shares of common stock available for issuance under the Plan from 630,662 shares to 1,866,009 shares.

In connection with the Company's IPO, the Board adopted and the Company's stockholders approved the 2018 Stock Option and Incentive Plan ("2018 Plan"), which became effective on the date immediately preceding the date on which the Company's registration statement became effective. The 2018 Plan provides for the grant of incentive stock options, non-statutory stock options, restricted stock awards, restricted stock units, stock appreciation rights, and other stock-based awards. The Company's employees, officers, directors, consultants and advisors are eligible to receive awards under the 2018 Plan. The number of shares of common stock that are reserved for issuance under the 2018 Plan are 2,200,260 shares. The 2018 Plan provides that the number of shares reserved and available for issuance under the plan will automatically increase each January 1, beginning on January 1, 2019, by 4% of the outstanding number of shares of the Company's common stock on the immediately preceding December 31 or such lesser number of shares as determined by the Board.

Since the date of effectiveness of the 2018 Plan, the Company has not and will not grant any further awards under the 2017 Plan. However, any shares of common stock subject to awards under the 2017 Plan that expire, terminate, or otherwise are surrendered, canceled, forfeited or repurchased without having been fully exercised or resulting in any common stock being issued will become available for issuance under the 2018 Plan. As of December 31, 2018, no such shares became available for issuance under the 2018 Plan.

Stock-based Compensation Expense

Total stock-based compensation expense is recognized for stock-based awards granted to employees and non-employees and has been reported in the Company's consolidated statements of operations and comprehensive loss as follows:

	Year Ended December 31, 2018	Year Ended December 31, 2017	July 5, 2016 (inception) through December 31, 2016
		(In thousands)	
Research and development	$ 1,236	$ 246	$ —
General and administrative	1,557	224	—
Total stock-based compensation expense	$ 2,793	$ 470	$ —

Stock Options

The following table summarizes stock option activity under the Plan:

	Shares Available for Grant	Number of Options Outstanding	Weighted-Average Exercise Price per Option	Weighted-Average Remaining Contract Term	Aggregate Intrinsic Value
					(In thousands)
Outstanding, December 31, 2017	1,670,341	195,668	$ 4.49	9.67	
Shares reserved for issuance	641,239				
Options granted(1)	(934,038)	934,038	13.05		
Restricted stock granted	(2,000)				
Restricted stock units granted	(24,960)				
Options exercised		(7,029)	0.79		
Outstanding, December 31, 2018	1,350,582	1,122,677	11.63	9.22	$ 818
Exercisable, December 31, 2018		67,613	6.32	8.74	241
Vested and expected to vest, December 31, 2018		1,122,677	11.63	9.22	818

(1) The Company granted 7,200 stock options to non-employees during the year ended December 31, 2018.

The aggregate intrinsic values of options outstanding, exercisable, vested and expected to vest were calculated as the difference between the exercise price of the options and the fair value of the Company's common stock as of December 31, 2018. The aggregate intrinsic values of options exercised during the year ended December 31, 2018 was $78,000. No options were exercised during the year ended December 31, 2017 and during the period from July 5, 2016 (inception) to December 31, 2016. No options were cancelled or forfeited during the years ended December 31, 2018 and 2017 and during the period from July 5, 2016 (inception) to December 31, 2016.

During the year ended December 31, 2018, the Company granted options to employees and directors to purchase an aggregate of 926,838 common shares with a weighted-average grant date fair value of $9.23. During the year ended December 31, 2017, the Company granted options to employees to purchase an aggregate of 148,808 common shares with a weighted-average grant date fair value of $3.75. During the year ended December 31, 2018, the Company granted options to non-employees to purchase an aggregate of 7,200 common shares with a weighted-average grant date fair value of $12.51. During the year ended December 31, 2017, the Company granted options to non-employees to purchase an aggregate of 46,860 common shares with a weighted-average grant date fair value of $0.67. On December 1, 2017, a non-employee became an employee of the Company. The expense related to options granted to employees and directors was $1.7 million and $28,000 for the years ended December 31, 2018 and 2017, respectively. The expense related to options granted to non-employees was $0.1 million and $59,000 for the years ended December 31, 2018 and 2017, respectively. There were no stock options granted to employees or non-employees during the period from July 5, 2016 (inception) to December 31, 2016.

As of December 31, 2018, the total unrecognized compensation expense related to unvested employee options was $7.5 million which the Company expects to recognize over an estimated weighted-average period of 3.17 years. As of December 31, 2018, the total unrecognized compensation expense related to unvested non-employee options was $0.1 million which the Company expects to recognize over an estimated weighted-average period of 2.67 years.

The fair value of stock options for employees and non-employees was estimated using a Black-Scholes option pricing model with the following assumptions:

	Year Ended December 31,	
	2018	2017
Employees:		
Fair value of common stock	$8.57 - $15.45	$0.79 - $9.33
Expected term (in years)	5.8 - 6.2	5.9 - 6.2
Expected volatility	75.9% - 90.6%	74.4% - 74.5%
Risk-free interest rate	2.4% - 3.1%	1.9% - 2.2%
Expected dividend yield	0.0%	0.0%
Non-employees:		
Fair value of common stock	$8.62 - $15.45	$0.79 - $10.28
Expected term (in years)	10.0 - 8.50	10.0 - 9.4
Expected volatility	78.0% - 91.2%	74.6% - 77.0%
Risk-free interest rate	2.7% - 3.1%	2.3% - 2.4%
Expected dividend yield	0.0%	0.0%

Fair Value of Common Stock: Prior to the IPO, given the absence of a public trading market, the Board of Directors considered numerous objective and subjective factors to determine the fair value of common stock at each grant date. These factors included, but were not limited to, (i) contemporaneous valuations of common stock performed by independent third-party specialists; (ii) the prices for preferred stock sold to outside investors; (iii) the rights, preferences and privileges of preferred stock relative to common stock; (iv) the lack of marketability of common stock; (v) developments in the business; and (vi) the likelihood of achieving a liquidity event, such as an initial public offering or a merger or acquisition of the Company, given prevailing market conditions.

Restricted Stock

On July 11, 2016, certain founding non-employee directors purchased 3,772,726 common shares that are subject to a repurchase right upon termination or cessation of services at the original purchase price of $0.0001 per share, or $483. Compensation expense of such unvested shares was remeasured at fair value until vested at each reporting date. On April 4, 2017, the non-employee directors became employees of the Company and as a result, compensation expense of the unvested shares was remeasured at fair value and fixed and was being recognized over the remaining vesting period. Upon the closing of the Series A preferred financing, a portion of the unvested shares accelerated and vested in full. Upon the Company's IPO, the remaining unvested shares accelerated and vested in full.

On April 17, 2018, the Company granted 2,000 shares of restricted stock to a consultant. The restrictions will lapse in four equal quarterly installments and will be fully vested on the first anniversary of such grant. Compensation expenses of such unvested shares will be remeasured at fair value until vested at each reporting date.

The summary of restricted stock activity and related information follows:

	Number of Restricted Shares Outstanding
Unvested shares — December 31, 2017	1,096,449
Granted	2,000
Vested	(1,097,449)
Unvested shares — December 31, 2018	1,000

The Company recognized $0.9 million, $0.4 million and $0 of stock-based compensation expense related to restricted shares during the years ended December 31, 2018 and 2017 and the period from July 5, 2016 (inception) to December 31, 2016, respectively. As of December 31, 2018, there was $3,000 of unrecognized stock-based compensation expense related to unvested restricted stock. This amount is expected to be recognized over a remaining weighted-average period of 0.29 years.

Restricted Stock Units

During the year ended December 31, 2018, the Company granted 24,960 restricted stock units to an employee with a weighted-average grant date fair value of $9.03 per share.

The summary of restricted stock unit activity and related information follows:

	Number of Restricted Stock Units Outstanding
Unvested shares — December 31, 2017	—
Granted	24,960
Unvested shares — December 31, 2018	24,960

The Company recognized $35,000, $0 and $0 of stock-based compensation expense related to restricted stock units during the years ended December 31, 2018 and 2017 and the period from July 5, 2016 (inception) to December 31, 2016, respectively. As of December 31, 2018, there was $0.2 million of unrecognized stock-based compensation expense related to unvested restricted stock units. This amount is expected to be recognized over a remaining weighted-average period of 3.39 years. There were no restricted stock units granted to employees or non-employees during the year ended December 31, 2017 and the period from July 5, 2016 (inception) to December 31, 2016.

2018 Employee Stock Purchase Plan

The Board adopted and the Company's stockholders approved the 2018 Employee Stock Purchase Plan ("2018 ESPP"), which became effective on the date immediately preceding the date on which the Company's registration statement became effective. The 2018 ESPP enables eligible employees to purchase shares of the Company's Common Stock at a discount. The number of shares of common stock that are reserved for issuance under the 2018 ESPP are 275,030 shares. The 2018 ESPP provides that the number of shares reserved and available for issuance will automatically increase each January 1, beginning on January 1, 2019 and increasing each January 1 thereafter through January 1, 2028, by the least of (i) 1% of the outstanding number of shares of the Company's common stock on the immediately preceding December 31; (ii) 543,926 shares or (iii) such number of shares as determined by the ESPP administrator.

11. Income Taxes

Provision for Income Taxes

For the years ended December 31, 2018 and 2017 and the period from July 5, 2016 (inception) to December 31, 2016, the Company did not record a current or deferred income tax expense. The Company's consolidated loss before income taxes consists solely of a domestic loss.

A reconciliation of income tax expense computed at the statutory federal income tax rate to income taxes as reflected in the consolidated financial statements is as follows:

	Year Ended December 31, 2018	Year Ended December 31, 2017	July 5, 2016 (inception) through December 31, 2016
	(In thousands)		
Income tax expense (benefit) at federal statutory rate	$ (7,899)	$ (11,484)	$ —
State taxes	(2,340)	(1,011)	—
Tax credits	(817)	(222)	—
Stock-based compensation	764	140	—
Federal tax rate change	—	2,202	—
Change in fair value of tranche rights	3	5,065	—
Other	241		—
Change in valuation allowance	10,074	5,310	—
Income tax expense	$ 26	$ —	$ —
Effective tax rate	0.0%	0.0%	0.0%

On December 22, 2017, the Tax Cuts and Jobs Act ("TCJA") was signed into United States law. The TCJA includes a number of changes to existing tax law, including, among other things, a permanent reduction in the federal corporate income tax rate from 34% to 21%, effective as of January 1, 2018, as well as limitation of the deduction for net operating losses to 80% of annual taxable income and elimination of net operating loss carrybacks, in each case, for losses arising in taxable years beginning after December 31, 2017 (though any such net operating losses may be carried forward indefinitely). The tax rate change resulted in (i) a reduction in the gross amount of our deferred tax assets as of December 31, 2017, without an impact on the net amount of our deferred tax assets, which are recorded with a full valuation allowance, and (ii) no income tax expense or benefit being recognized as of the enactment date of the TCJA.

Deferred Tax Assets and Liabilities

Deferred income taxes reflect the net tax effects of loss and credit carryforwards and temporary differences between the carrying amounts of assets and liabilities for financial reporting purposes and the amounts used for income tax purposes. Significant components of deferred income taxes were as follows as of December 31, 2018 and 2017:

	As of December 31,	
	2018	2017
	(In thousands)	
Deferred tax assets:		
Net operating losses	$ 13,054	$ 3,953
Capitalized license	869	896
Research credits	1,007	269
Accruals	514	176
Stock-based compensation	51	16
Total gross deferred tax assets	15,495	5,310
Less valuation allowance	(15,373)	(5,310)
Total deferred tax assets	122	—
Deferred tax liabilities:		
Other comprehensive income - unrealized loss	11	
Depreciation and amortization	111	—
Total gross deferred tax liability	122	—
Net deferred tax assets	$ —	$ —

Realization of deferred tax assets is dependent upon future earnings, if any, the timing and amount of which are uncertain. Due to the lack of earnings history, the net deferred tax assets have been fully offset by a valuation allowance. A valuation allowance of $15.4 million and $5.3 million has been recorded for the years ended December 31, 2018 and 2017, respectively.

Net Operating Loss and Tax Credit Carryforwards

As of December 31, 2018 and 2017, the Company had net operating loss carryforwards for federal income tax purposes of approximately $47.3 million and $14.5 million, respectively which will begin to expire in 2036. As of December 31, 2018 and 2017, the Company had total state net operating loss carryforwards of approximately $49.4 million and $14.4 million, respectively which will begin to expire in 2036. Utilization of some of the federal and state net operating loss and credit carryforwards are subject to annual limitations due to the "change of ownership" provisions under Sections 382 and 383 of the Internal Revenue Code of 1986, as amended, and similar state provisions. The annual limitations may result in the expiration of net operating losses and credits before utilization. The Company has not performed an ownership change analysis.

As of December 31, 2018 and 2017, the Company had federal research credits of $0.9 million and $0.2 million, respectively, which will begin to expire in 2037 and state research credits of $0.2 million and $60,000, respectively, which will begin to expire in 2032. These tax credits are subject to the same limitations discussed above.

Unrecognized Tax Benefits

The Company has incurred net operating losses since inception and has no significant unrecognized tax benefits. If in the future the Company recognizes uncertain tax positions, the Company's effective tax rate will be reduced. Currently, the Company has a full valuation allowance against its net deferred tax asset which would impact the timing of the effective tax rate benefit should any of these uncertain tax positions be favorably settled in the future. Any adjustments to uncertain tax positions would result in an adjustment of net operating loss or tax credit carry forwards rather than resulting in a cash outlay. As of December 31, 2018, the Company had no unrecognized tax benefits and no accrued interest or penalties related to uncertain tax positions.

Income tax returns are filed in the U.S. and Massachusetts. The Company is not currently under examination. Due to net operating losses and research credit carryovers, all of the tax years remain open to examination.

12. Commitments and Contingences

Litigation

The Company is not a party to any litigation and does not have contingency reserves established for any litigation liabilities as of December 31, 2018.

Lease

On January 3, 2018, the Company entered a lease for office space. The lease commencement date is January 1, 2018 and the lease expiration date is February 28, 2021. The Company paid $0.2 million and $0 in rent for years ended December 31, 2018 and 2017, respectively. Obligations to make future minimum lease payments at December 31, 2018, are as follows (in thousands):

Year ending December 31,	Minimum Lease Payments
2019	$ 231
2020	236
2021	39
Total	$ 506

Novartis License Agreement

The Company is required to pay up to an aggregate of $4.3 million upon the satisfaction of clinical milestones, up to an aggregate of $24 million upon the satisfaction of regulatory milestones for the first indication approved, and up to an aggregate of $18 million upon the satisfaction of regulatory milestones for the second indication approved. In addition, the Company is required to pay up to an aggregate of $125 million upon the satisfaction of commercial milestones, based on the amount of annual net sales. The Company is also required to pay tiered royalties ranging from a mid single-digit percentage to a low teen-digit percentage on annual net sales of products. These royalty obligations last on a product-by-product and country-by-country basis until the latest of (i) the expiration of the last valid claim of a Novartis patent covering a subject product, (ii) the expiration of any regulatory exclusivity for the subject product in a country, or (iii) the 10th anniversary of the first commercial sale in the country, and are subject to a reduction after the expiration of the last valid claim of a Novartis patent or the introduction of a generic equivalent of a product in a country.

Silverstein Foundation

The Company is obligated to repay the Funding Amount in full to the Silverstein Foundation if it successfully conducts a positive Phase 3 clinical trial of the Product for Parkinson's Disease (see Note 7).

13. Net Loss per Share

As described in Note 2, the Company computes basic and diluted earnings (losses) per share using a methodology that gives effect to the impact of outstanding participating securities (the "two-class" method). Basic net loss per share is calculated by dividing net loss by the weighted-average number of common shares outstanding during the period and excludes any dilutive effects of share-based awards. Diluted net loss per share is computed giving effect to all potential dilutive common shares, including common stock issuable upon exercise of stock options, convertible preferred stock, and unvested restricted common stock. As the Company had net losses for the years ended December 31, 2018 and 2017 and the period from July 5, 2016 (inception) to December 31, 2016, there is no income allocation required under the two-class method or dilution attributed to weighted average shares outstanding in the calculation of diluted loss per share.

14. Related Party Transactions

Since the Company's incorporation in July 2016, the Company has engaged in transactions with related parties.

During the year ended December 31, 2017, the Company issued 1,886,363 shares of common stock and made payments to PureTech for certain founding services and cost reimbursements. PureTech is a founder of the Company and holds shares of common stock and preferred stock of the Company (See Note 8).

The Company is a party to an intellectual property license agreement with Novartis. In addition, NIBR is a preferred stock shareholder of the Company (See Note 6). During the year ended December 31, 2017, the Company made payments to Novartis for milestones achieved pursuant to the license agreement and for the purchases of materials for use in the Company's clinical trials. No payments have been made to Novartis during the year ended December 31, 2018.

Aggregate payments for the above related party transactions totaled $0, $0.9 million and $0 for the years ended December 31, 2018 and 2017 and period from July 5, 2016 (inception) to December 31, 2016, respectively.

The Company is a party to a Funding Agreement with the Silverstein Foundation, an entity in which one of the Company's directors is a co-founder and current trustee (See Note 7). The Company received $0.5 million from the Silverstein Foundation during the year ended December 31, 2018. No funds were received during the year ended December 31, 2017 and the period from July 5, 2016 (inception) to December 31, 2016.

15. Selected Quarterly Financial Data (Unaudited)

The following table contains quarterly financial information for 2018 and 2017. The Company believes that the following information reflects all normal recurring adjustments necessary for a fair statement of the information for the periods presented. The operating results for any quarter are not necessarily indicative of results for any future period.

	2018				
	First Quarter	Second Quarter	Third Quarter	Fourth Quarter	Total
	(in thousands, except per share data)				
Total operating expenses	$ 10,200	$ 14,113	$ 9,032	$ 6,360	$ 39,705
Loss from operations	(10,200)	(14,113)	(9,032)	(6,360)	(39,705)
Net loss	(9,859)	(13,591)	(8,407)	(5,757)	(37,614)
Net loss applicable to common stockholders	(9,859)	(13,591)	(8,407)	(5,757)	(37,614)
Net loss per share applicable to common stockholders—basic and diluted	$ (0.46)	$ (0.48)	$ (0.30)	$ (0.21)	$ (1.42)

	2017				
	First Quarter	Second Quarter	Third Quarter	Fourth Quarter	Total
	(in thousands, except per share data)				
Total operating expenses	$ 3,357	$ 4,057	$ 3,945	$ 7,523	$ 18,882
Loss from operations	(3,357)	(4,057)	(3,945)	(7,523)	(18,882)
Net loss	(3,357)	(4,057)	(3,310)	(23,054)	(33,778)
Net loss applicable to common stockholders	(3,357)	(4,057)	(3,310)	(23,054)	(33,778)
Net loss per share applicable to common stockholders—basic and diluted	$ (1.20)	$ (0.94)	$ (0.75)	$ (5.11)	$ (8.42)

PART IV

Item 15. Exhibits and Financial Statement Schedules.

(a) The following documents are included in this Annual Report on Form 10-K:

(1) The following Report and Consolidated Financial Statements of the Company are included in this Annual Report:

Report of Independent Registered Public Accounting Firm

Consolidated Balance Sheets

Consolidated Statements of Operations and Comprehensive Loss

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

Consolidated Statements of Cash Flows

Notes to Consolidated Financial Statements

(2) Financial Statement Schedules:

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

(3) Exhibits. The exhibits filed as part of this Annual Report on Form 10-K are set forth on the Exhibit Index immediately preceding the signature page of this Annual Report on Form 10-K. The Exhibit Index is incorporated herein by reference.

Item 16. 10-K Summary

The Company has elected not to include summary information.

EXHIBIT INDEX

Exhibit Number	Description of Exhibit
3.1	Third Amended and Restated Certificate of Incorporation of the Registrant (as currently in effect) (incorporated by reference to Exhibit 3.1 to the Registrant's Current Report on Form 8-K (File No. 001-38359) filed with the SEC on January 30, 2018)
3.2	Amended and Restated Bylaws of the Registrant (as currently in effect) (incorporated by reference to Exhibit 3.2 to the Registrant's Current Report on Form 8-K (File No. 001-38359) filed with the SEC on January 30, 2018)
4.1	Specimen stock certificate evidencing the shares of common stock (incorporated by reference to Exhibit 4.1 to the Registrant's Registration Statement on Form S-1, as amended, (File No. 333-222373) filed with the SEC on January 16, 2018)
4.2	Amended and Restated Investors' Rights Agreement, dated as of November 29, 2017, among the Registrant and the other parties thereto (incorporated by reference to Exhibit 4.1 to the Registration Statement on Form S-1 (File No. 333-222373) filed with the SEC on December 29, 2017)
10.1#	2017 Stock Incentive Plan and forms of award agreements thereunder (incorporated by reference to Exhibit 10.1 to the Registrant's Registration Statement on Form S-1, as amended, (File No. 333-222373) filed with the SEC on January 16, 2018)
10.2#	2018 Stock Option and Incentive Plan and forms of award agreements thereunder (incorporated by reference to Exhibit 10.2 to the Registrant's Registration Statement on Form S-1, as amended, (File No. 333-222373) filed with the SEC on January 16, 2018)
10.3#	Form of Director and Officer Indemnification Agreement (incorporated by reference to Exhibit 10.3 to the Registrant's Registration Statement on Form S-1, as amended, (File No. 333-222373) filed with the SEC on January 16, 2018)
10.4#	Form of Officer Indemnification Agreement (incorporated by reference to Exhibit 10.4 to the Registrant's Registration Statement on Form S-1, as amended, (File No. 333-222373) filed with the SEC on January 16, 2018)
10.5#	2018 Employee Stock Purchase Plan (incorporated by reference to Exhibit 10.5 to the Registrant's Registration Statement on Form S-1, as amended, (File No. 333-222373) filed with the SEC on January 16, 2018)
10.6#	Non-Employee Director Compensation Policy (incorporated by reference to Exhibit 10.6 to the Registrant's Registration Statement on Form S-1, as amended, (File No. 333-222373) filed with the SEC on January 16, 2018)
10.7+	License Agreement, dated as of March 23, 2017, by and between the Registrant and Novartis International Pharmaceutical Ltd. (incorporated by reference to Exhibit 10.7 to the Registrant's Registration Statement on Form S-1, as amended, (File No. 333-222373) filed with the SEC on January 16, 2018)
10.8+	First Amendment to License Agreement, dated as of October 3, 2017, by and among the Registrant and Novartis International Pharmaceutical Ltd. (incorporated by reference to Exhibit 10.5 to the Registrant's Registration Statement on Form S-1 (File No. 333-222373) filed with the SEC on December 29, 2017)
10.9	Business Services, Personnel and Information Management Agreement, dated as of August 1, 2016, by and among the Registrant, PureTech Management, Inc., PureTech Health LLC and PureTech Health plc (incorporated by reference to Exhibit 10.6 to the Registrant's Registration Statement on Form S-1 (File No. 333-222373) filed with the SEC on December 29, 2017)
10.10#	Offer Letter, dated as of March 31, 2017, between the Registrant and Chen Schor (incorporated by reference to Exhibit 10.7 to the Registrant's Registration Statement on Form S-1 (File No. 333-222373) filed with the SEC on December 29, 2017)

Exhibit Number	Description of Exhibit
10.11#	Offer Letter, dated as of March 31, 2017, between the Registrant and Joan Mannick (incorporated by reference to Exhibit 10.8 to the Registrant's Registration Statement on Form S-1 (File No. 333-222373) filed with the SEC on December 29, 2017)
10.12#	Offer Letter, dated as of October 5, 2017, between the Registrant and John McCabe (incorporated by reference to Exhibit 10.9 to the Registrant's Registration Statement on Form S-1 (File No. 333-222373) filed with the SEC on December 29, 2017)
10.13#	Amendment to Offer Letter, dated as of March 31, 2017, between the Registrant and Joan Mannick (incorporated by reference to Exhibit 10.13 to the Registrant's Registration Statement on Form S-1, as amended, (File No. 333-222373) filed with the SEC on January 16, 2018)
10.14#	Amendment to Offer Letter, dated as of March 31, 2017, between the Registrant and Chen Schor (incorporated by reference to Exhibit 10.14 to the Registrant's Registration Statement on Form S-1, as amended, (File No. 333-222373) filed with the SEC on January 16, 2018)
10.15	Office Lease Agreement, dated as of January 8, 2018, by and between the Registrant and 500 Boylston and 222 Berkeley Owner (DE) LLC (incorporated by reference to Exhibit 10.12 to the Registrant's Registration Statement on Form S-1, as amended, (File No. 333-222373) filed with the SEC on January 16, 2018)
10.16#	Senior Executive Cash Incentive Bonus Plan (incorporated by reference to Exhibit 10.16 of the Registrant's Annual Report on Form 10-K (File No. 001-38359) filed with the SEC on March 29, 2018)
10.17#	Employment Agreement, dated as of August 30, 2018, by and between the Registrant and Meredith S. Manning (incorporated by reference to Exhibit 10.1 to the Registrant's Quarterly Report on Form 10-Q (File No. 001-38359) filed with the SEC on November 13, 2018)
21.1*	Subsidiaries of the Registrant
23.1*	Consent of KPMG LLP, independent registered public accounting firm
31.1*	Certification of Principal Executive Officer pursuant to Rule 13a-14(a) and Rule 15d-14(a) of the Securities Exchange Act of 1934, as adopted pursuant to Section 302 of the Sarbanes-Oxley Act of 2002
31.2*	Certification of Principal Financial Officer pursuant to Rule 13a-14(a) and Rule 15d-14(a) of the Securities Exchange Act of 1934, as adopted pursuant to Section 302 of the Sarbanes-Oxley Act of 2002
32.1**	Certification of Principal Executive Officer and Principal Financial Officer pursuant to 18 U.S.C. §1350, as adopted pursuant to Section 906 of the Sarbanes-Oxley Act of 2002
101.INS*	XBRL Instance Document
101.SCH*	XBRL Taxonomy Extension Schema Document
101.CAL*	XBRL Taxonomy Extension Calculation Linkbase Document
101.DEF*	XBRL Taxonomy Extension Definition Linkbase Document
101.LAB*	XBRL Taxonomy Extension Label Linkbase Document
101.PRE*	XBRL Taxonomy Extension Presentation Linkbase Document

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* Filed herewith.

\+ Confidential treatment granted as to certain portions, which portions have been omitted and filed separately with the Securities and Exchange Commission.

\# Indicates a management contract or any compensatory plan, contract or arrangement.

** The certifications furnished in Exhibit 32.1 hereto are deemed to accompany this Annual Report on Form 10-K and will not be deemed "filed" for purposes of Section 18 of the Securities Exchange Act of 1934, as amended. Such certifications will not be deemed to be incorporated by reference into any filings under the Securities Act of 1933, as amended, or the Securities Exchange Act of 1934, as amended, except to the extent that the Registrant specifically incorporates it by reference.

SIGNATURES

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

resTORbio, Inc.

Date: March 18, 2019

By: /s/ Chen Schor
Chen Schor
President, Chief Executive Officer and Director
(Principal Executive Officer)

Pursuant to the requirements of the Securities Act of 1934, this Annual Report on Form 10-K has been signed by the following persons in the capacities and on the dates indicated.

Signature	Title	Date
/s/ Chen Schor Chen Schor	President, Chief Executive Officer and Director (principal executive officer)	March 18, 2019
/s/ John McCabe John McCabe	Vice President, Finance (principal financial officer and principal accounting officer)	March 18, 2019
/s/ Jeffrey Chodakewitz Jeffrey Chodakewitz	Director	March 18, 2019
/s/ Paul Fonteyne Paul Fonteyne	Director	March 18, 2019
/s/ Michael Grissinger Michael Grissinger	Director	March 18, 2019
/s/ Jonathan Silverstein Jonathan Silverstein	Director	March 18, 2019
/s/ David Steinberg David Steinberg	Director	March 18, 2019
/s/ Lynne Sullivan Lynne Sullivan	Director	March 18, 2019

Exhibit 21.1

SUBSIDIARIES

Subsidiary	Jurisdiction of Incorporation
resTORbio Securities Corp.	Massachusetts

Exhibit 23.1

Consent of Independent Registered Public Accounting Firm

The Board of Directors
resTORbio, Inc.:

We consent to the incorporation by reference in the registration statement (No. 333-222746) on Form S-8 and in registration statement (No. 333-229499) on Form S-3 of resTORbio, Inc. of our report dated March 18, 2019, with respect to the consolidated balance sheets of resTORbio, Inc. as of December 31, 2018 and 2017, the related consolidated statements of operations and comprehensive loss, redeemable convertible preferred stock and stockholders' equity (deficit), and cash flows for the years ended December 31, 2018 and 2017 and the period July 5, 2016 (inception) through December 31, 2016, and the related notes, which report appears in the December 31, 2018 annual report on Form 10-K of resTORbio, Inc..

/s/ KPMG LLP

Cambridge, Massachusetts
March 18, 2019

Exhibit 31.1

CERTIFICATION OF PRINCIPAL EXECUTIVE OFFICER PURSUANT TO RULE 13a-14(a) / RULE 15d-14(a) OF THE SECURITIES EXCHANGE ACT OF 1934, AS AMENDED

I, Chen Schor, certify that:

1. I have reviewed this Annual Report on Form 10-K of resTORbio, 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)AA 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.

/s/ Chen Schor

Chen Schor
President and Chief Executive Officer
(Principal Executive Officer)

Dated: March 18, 2019

Exhibit 31.2

CERTIFICATION OF PRINCIPAL FINANCIAL OFFICER PURSUANT TO RULE 13a-14(a) / RULE 15d-14(a) OF THE SECURITIES EXCHANGE ACT OF 1934, AS AMENDED

I, John J. McCabe, certify that:

1. I have reviewed this Annual Report on Form 10-K of resTORbio, 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.

/s/ John J. McCabe

John J. McCabe
Vice President, Finance
(Principal Financial and Accounting Officer)

Dated: March 18, 2019

Exhibit 32.1

CERTIFICATIONS OF PRINCIPAL EXECUTIVE OFFICER AND PRINCIPAL FINANCIAL OFFICER 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 resTORbio, Inc. (the "Company") for the fiscal year ended December 31, 2018 as filed with the Securities and Exchange Commission on the date hereof (the "Report"), the undersigned hereby certify, pursuant to 18 U.S.C. Section 1350, that, to the best of their knowledge:

(1) the Report fully complies with the requirements of Section 13(a) or 15(d) of the Securities Exchange Act of 1934, as amended; and

(2) the information contained in the Report fairly presents, in all material respects, the financial condition and results of operations of the Company.

/s/ Chen Schor

Chen Schor
President and Chief Executive Officer
(Principal Executive Officer)

Dated: March 18, 2019

/s/ John J. McCabe

John J. McCabe
Vice President, Finance
(Principal Financial and Accounting Officer)

Dated: March 18, 2019