UNITED STATES
SECURITIES AND EXCHANGE COMMISSION
WASHINGTON, D.C. 20549

FORM 10-K

(Mark One)

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

For the fiscal year ended December 31, 2018

OR

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

For the transition period from to

Commission File Number: 001-38586

RUBIUS THERAPEUTICS, INC.
(Exact name of registrant as specified in its charter)

Delaware	**46-2688109**
(State or other jurisdiction of incorporation or organization)	(I.R.S. Employer Identification No.)
399 Binney Street, Suite 300 Cambridge, Massachusetts	**02139**
(Address of principal executive offices)	(Zip code)

(617) 679-9600
(Registrant's telephone number, including area code)

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

Title of each class	Name of exchange on which registered
Common Stock, $0.001 Par Value	**NASDAQ Global Select Market**

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

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

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

Indicate by check mark whether the registrant (1) has filed all reports required to be filed by Section 13 or 15(d) of the Securities Exchange Act of 1934 during the preceding 12 months (or for such shorter period that the registrant was required to file such reports), and (2) has been subject to such filing 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, a smaller reporting company, or an emerging growth company. See the definitions of "large accelerated filer," "accelerated filer," "smaller reporting company," and "emerging growth company" in Rule 12b-2 of the Exchange Act.

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

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

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

As of June 29, 2018, the last business day of the registrant's most recently completed second fiscal quarter, there was no established public market for the registrant's common stock. The registrant's common stock began trading on the NASDAQ Global Select Market on July 18, 2018. The aggregate market value of common stock held by non-affiliates of the registrant computed by reference to the price of the registrant's common stock as of July 18, 2018 (based on the last reported sale price on the NASDAQ Global Select Market as of such date) was $718.9 million.

As of February 28, 2019, the registrant had 79,529,965 shares of common stock, $0.001 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, 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.

Rubius Therapeutics, Inc.
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FORWARD-LOOKING STATEMENTS

This Annual Report on Form 10-K contains forward-looking statements, which reflect our current views with respect to, among other things, our operations and financial performance. 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, plan, objectives of management and expected market growth are forward-looking statements. You can identify these forward-looking statements by the use of words such as "outlook," "believes," "expects," "potential," "continues," "may," "will," "should," "seeks," "approximately," "predicts," "intends," "plans," "estimates," "anticipates" or the negative version of these words or other comparable words. Such forward-looking statements are subject to various risks and uncertainties. Accordingly, there are or will be important factors that could cause actual outcomes or results to differ materially from those indicated in these statements. We believe these factors include but are not limited to those described under "Risk Factors" and include, among other things:

- the success, cost and timing of our product development activities and clinical trials, including statements regarding the timing of initiation and completion of studies or trials and related preparatory work, the period during which the results of the trials will become available, and our research and development programs;
- our ability to advance any product candidate into or successfully complete any clinical trial;
- our ability or the potential to successfully manufacture our product candidates for clinical trials or for commercial use, if approved;
- our plans to renovate, customize and operate our recently purchased manufacturing facility;
- the potential for our identified research priorities to advance our technologies;
- our ability to maintain regulatory approval, if obtained, of any of our current or future product candidates, and any related restrictions, limitations and/or warnings in the label of an approved product candidate;
- the ability to license additional intellectual property relating to our product candidates and to comply with our existing license agreements;
- our ability to commercialize our products in light of the intellectual property rights of others;
- developments relating to cellular therapies, including red blood cell therapies;
- the success of competing therapies that are or become available;
- our ability to obtain funding for our operations, including funding necessary to complete further development and commercialization of our product candidates;
- the commercialization of our product candidates, if approved;
- our plans to research, develop and commercialize our product candidates;
- our ability to attract collaborators with development, regulatory and commercialization expertise;
- future agreements with third parties in connection with the commercialization of our product candidates and any other approved product;
- the size and growth potential of the markets for our product candidates, and our ability to serve those markets;

- the rate and degree of market acceptance of our product candidates;
- regulatory developments in the United States and foreign countries;
- our ability to contract with third-party suppliers and manufacturers and their ability to perform adequately;
- our ability to attract and retain key scientific or management personnel;
- the accuracy of our estimates regarding expenses, future revenue, capital requirements and needs for additional financing;
- the impact of laws and regulations;
- our expectations regarding our ability to obtain and maintain intellectual property protection for our product candidates;
- our expectations regarding the period during which we qualify as an "emerging growth company" under the Jumpstart Our Business Startups Act; and
- our use of the proceeds from the initial public offering.

All of our forward-looking statements are as of the date of this Annual Report on Form 10-K only. In each case, actual results may differ materially from such forward-looking information. We can give no assurance that such expectations or forward-looking statements will prove to be correct. An occurrence of or any material adverse change in one or more of the risk factors or risks and uncertainties referred to in this Annual Report on Form 10-K or included in our other public disclosures or our other periodic reports or other documents or filings filed with or furnished to the Securities and Exchange Commission, or the SEC, could materially and adversely affect our business, prospects, financial condition and results of operations. Except as required by law, we do not undertake or plan to update or revise any such forward-looking statements to reflect actual results, changes in plans, assumptions, estimates or projections or other circumstances affecting such forward-looking statements occurring after the date of this Annual Report on Form 10-K, even if such results, changes or circumstances make it clear that any forward-looking information will not be realized. Any public statements or disclosures by us following this Annual Report on Form 10-K that modify or impact any of the forward-looking statements contained in this Annual Report on Form 10-K will be deemed to modify or supersede such statements in this Annual Report on Form 10-K.

PART I

Except where the context otherwise requires or where otherwise indicated, the terms "Rubius," "Rubius Therapeutics," "we," "us," "our," "our company," "the company," and "our business" refer to Rubius Therapeutics, Inc. and its consolidated subsidiary.

Item 1. Business

We are developing a new class of cellular medicines, Red Cell Therapeutics, or RCTs. Based on our vision that human red blood cells are the foundation of the next significant innovation in medicine, we have designed a proprietary platform to genetically engineer and culture RCTs that are selective, potent and ready-to-use cellular therapies. We believe that our RCTs will provide life-changing or life-saving benefits for patients with severe diseases across multiple therapeutic areas.

We have generated hundreds of RCTs using our RED PLATFORM®, a highly versatile and proprietary cellular therapy platform. We are utilizing our universal engineering and manufacturing processes to advance a broad pipeline of RCT product candidates into clinical trials in rare diseases, cancer and autoimmune diseases. Common design and manufacturing elements of our RCTs should enable us to achieve significant advantages in product development. We are establishing end-to-end manufacturing capabilities and plan to develop commercial infrastructure to further establish Rubius Therapeutics as a leading, fully integrated cellular therapy company.

Our RED PLATFORM builds upon the research and findings of Flagship Pioneering's VentureLabs innovation team along with the discoveries of Professors Harvey Lodish and Hidde Ploegh of the Whitehead Institute for Biomedical Research at MIT. This work demonstrated the ability to differentiate donor-derived CD34+ hematopoietic precursor cells into enucleated red blood cells, or RBCs, with unprecedented efficiency at a small, laboratory scale. Based on this foundation, Flagship Pioneering's VentureLabs innovation team recognized the potential for RBCs as an optimal framework for cellular therapies and invented methods to engineer RCTs to express biotherapeutic proteins within the cell or on the cell surface.

Building upon these early discoveries, we have developed the RED PLATFORM, which enables us to engineer and culture RCT product candidates with a wide array of biotherapeutic proteins and biological functions that enable their use across multiple therapeutic areas. We have also invested considerably to scale the process of RCT manufacturing by acquiring our own manufacturing facility, which we believe will allow for the production of large quantities of reliable and reproducible RCT products from the initial stages of development through to commercial scale. We have and continue to build a broad portfolio of patent applications, know how, trade secrets, and other intellectual property that covers both our platform technologies as well as product discoveries, the breadth and depth of which is a strategic asset that could provide us with competitive advantages. As of February 28, 2019, we own or have an exclusive license under more than 100 patent applications across 26 different patent families, and we own one issued U.S. patent related to the treatment of phenylketonuria, or PKU.

Although our RCT product candidates are in early stages of development and will require substantial resources to demonstrate technical feasibility and to establish clinical and regulatory validation, we believe that our RED PLATFORM could provide beneficial treatments for our target indications, many of which have few, if any, effective treatments. Our initial focus will be advancing RCT product candidates with unique benefits for patients with rare diseases, cancer and autoimmune diseases based on three modalities — cellular shielding, potent cell-cell interaction and tolerance induction. In March 2019, we announced that the FDA cleared our investigational new drug, or IND, application for our lead product candidate, RTX-134, an RCT with the phenylalanine ammonia lyase (PAL) enzyme expressed within the cell for the treatment of phenylketonuria.

- **Rare Diseases:** We engineer RCTs that express potent enzymes within the cell for the treatment of patients suffering from rare enzyme deficiency diseases. As they are located within the RCT, these enzymes are shielded from being neutralized by the immune system, thereby allowing the enzymes to degrade and clear the pathogenic metabolites that build up in such diseases. We believe these RCTs may have a longer and sustained treatment duration and could avoid the immune-driven reduction in efficacy and induction of adverse events associated with other therapies.

- **Cancer:** We engineer RCTs to recapitulate human immunobiology via potent cell-cell interaction by expressing hundreds of thousands of copies of one or more proteins on the cellular surface to drive enhanced and synergistic activation of both the adaptive and innate immune systems in an antigen-specific approach or by broadly stimulating both arms of the immune system. We believe that these characteristics will translate into potent anti-tumor activity and limited off tissue adverse effects, because RCTs are generally confined to the vasculature and therefore, could be transformative therapies for patients with solid and hematological cancers.

- **Autoimmune Diseases:** We engineer RCTs that express specific autoimmune disease associated antigens within the cell or on the cell surface in order to induce and restore immune tolerance. We believe these RCTs could prevent immune damage that causes these diseases.

Our product candidates are allogeneic, making them ready-to-use, and we expect them to have a predictable biodistribution and an approximate circulation time of up to 120 days, which should enable us to deliver well-tolerated and convenient cellular therapies to a broad population.

We are developing our initial RCT product candidates for PKU, a wide range of solid and hematological cancers and autoimmune diseases. In March 2019, we announced that the FDA cleared our IND for RTX-134 for the treatment of PKU. We expect to begin enrolling patients for the Phase 1b clinical trial of RTX-134 during the second quarter of 2019, with initial data expected during the second half of 2019. We expect to file our first oncology IND for RTX-240 for the treatment of solid tumors by early 2020. We are in the early stages of assessing our RCT product candidates for the treatment of autoimmune diseases. We plan to file four to five INDs by the end of 2020, with additional filings thereafter.

Pending positive clinical data based on validated, approvable endpoints, we plan to advance these RCT product candidates as well as a broader portfolio of rare disease, cancer and autoimmune therapies toward registration. We plan to seek orphan drug designation as well as pursue breakthrough therapy or Regenerative Medicine Advanced Therapy, or RMAT, designations for our RCT portfolio where appropriate, which we believe may shorten the time to market.

Since we commenced operations in 2013, we have attracted a talented group of seasoned leaders to execute our strategy. Our leadership team has more than 200 years of combined experience at pharmaceutical and biotechnology companies, has been involved in filing more than a combined 80 INDs and 20 submissions for product approval and has launched more than 30 pharmaceutical products. We have raised approximately $498 million in private and public financings to date. We have also secured a credit facility that provides for up to $75 million in additional capital.

Utilizing RBCs to create cellular therapies

RBCs are the most ubiquitous cells in the human body, constituting over 80% of the body's cells and playing a critical role in the delivery of oxygen to tissues. To constantly replenish this population of critical cells, the human body generates approximately 2.5 million RBCs every second. RBCs represent the first example of a transformative cellular therapy as physicians have been transfusing blood to patients since the early 1800s. Today, the focus around cellular therapies has largely been directed toward T cell and other lymphocyte-based therapies. We believe that RBC-based therapies will transform the cellular therapy landscape as they may represent the ideal cell type for the creation of versatile, well-tolerated and ready-to-use cellular therapies. We believe such therapies could avoid many of the complications and risks often associated with earlier generation cellular therapies, including the emerging category of T cell-based therapies. These distinct characteristics of RBCs support their potential to serve as the foundation for a cellular therapy:

- a predictable circulating time of approximately 120 days;

- a well-characterized and controllable biodistribution as RBCs are generally sequestered in the vasculature, spleen and liver. In exceptional cases, RBCs may enter the tumor microenvironment via leaky neo-vasculature;

- the well-established use of O negative blood as a universal source that can be administered to greater than 95% of people;

- the presence of certain surface markers, such as CD47, on RBCs provide what are referred to as "don't eat me" signals, preventing the immune system from clearing RBCs from circulation; and

- since RBCs are enucleated, they do not pose a risk of uncontrolled cell division or oncogenicity following transfusion.

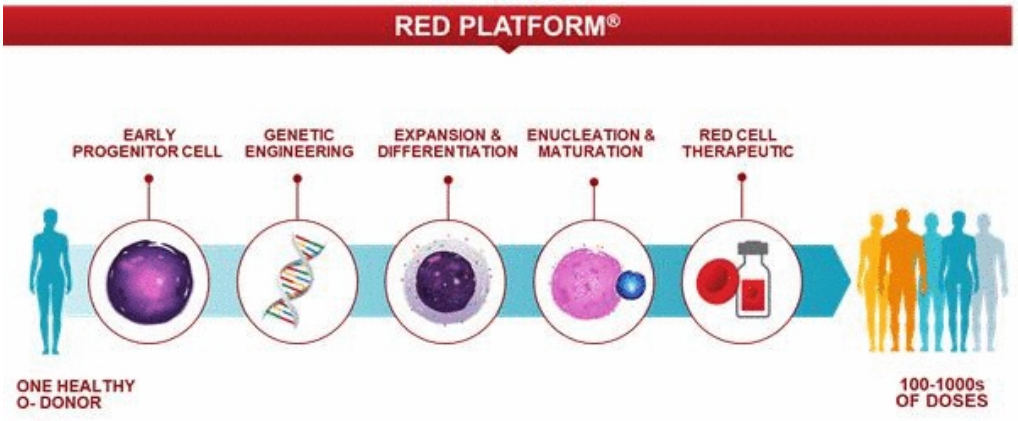
Today, blood transfusions remain one of the most commonly performed medical procedures, with approximately 85 million units of blood transfused worldwide each year. Significant infrastructure exists within most hospitals and outpatient infusion centers worldwide to support the administration of blood and blood-derived products. We intend to leverage this infrastructure to administer our products if approved.

Our proprietary RED PLATFORM

We are pioneering the creation of a new transformative class of medicines that leverage the benefits of RBCs to provide cellular therapies to patients with severe diseases across multiple therapeutic areas. As RBCs are enucleated, they have generally been considered simple oxygen delivery vehicles, rather than the backbone of a versatile cellular therapy platform. Past attempts at RBC-based therapies, such as applying hypotonic loading or cell swelling to load an enzyme or protein into RBCs, have had limited therapeutic applications, proven difficult to scale and reduced the *in vivo* half-life of the loaded RBCs.

Our discoveries and innovations in genetic engineering and cell culture processes have made it possible to now use RBCs as a foundation for the creation and development of a new class of cellular therapies. By modifying only one of our initial manufacturing steps in which we add a gene or genes that encode biotherapeutic proteins within the cell or on the cell surface of RCTs, we are able to rapidly develop new RCTs designed to treat different diseases. This approach allows for the consistent generation of product candidates and a preclinical evaluation process that we believe has the potential to create a broad range of therapeutics in an efficient manner — for example, RTX-134 required only nine months from product design to identification as our lead RCT product candidate. Our uniform approach should also enable us to leverage common chemistry, manufacturing and controls, or CMC, and toxicology data packages to shorten development timelines. While the initial focus of our RED PLATFORM will be in rare diseases, cancer and autoimmune diseases, we believe the versatility of our platform will enable us to expand into broader therapeutic areas in the future.

The RED PLATFORM allows us to generate a wide variety of allogeneic, ready-to-use RCT product candidates with a universal and proprietary process through the following steps: (1) obtaining CD34+ hematopoietic precursor cells from the blood of O negative donors; (2) genetic engineering of the cells to express biotherapeutic proteins within the cell or on the cell surface of the RCTs; (3) expanding the number of cells and differentiating them into reticulocytes, which are enucleated RBC precursors; and (4) formulating, characterizing and storing doses of the resulting RCT product candidate for later infusion into patients.



A significant advantage of differentiating the cells into reticulocytes is the ability to separate the genetic modification from the final RCT product candidate through the biological process of enucleation, a property unique to reticulocytes. Enucleation involves the ejection of the nucleus from the cell, and with it, all the DNA it contains, leaving behind an RCT that expresses the protein or proteins that confer the intended therapeutic benefit. We believe this absence of genetic material may reduce the safety risks associated with RCTs as compared with current cellular therapies.

Limitations of previous and current cellular therapies

The field of tissue, cell and regenerative therapy has a long history, starting with blood transfusions in the early 1800s, followed by organ and bone marrow transplants in the middle of the 20th century and later the approval of cellular therapy products ranging from epidermal transplantation for wound care to mesenchymal stem cells for the treatment of graft versus host disease and dendritic cells for the treatment of prostate cancer.

Most recently, several biotechnology companies and academic groups have demonstrated that a type of cell therapy known as chimeric antigen receptor T cells, or CAR-Ts, where a patient's own T cells are genetically engineered to recognize and attack specific cancer cells, are capable of powerful and sometimes curative therapeutic effects. In addition, some groups are studying the adoptive transfer and activation of T cell receptor, or TCR, -engineered T cells, and natural killer cells, or NK cells, for treatment of solid and hematologic cancers, while others are attempting to expand and engineer regulatory T cells *ex vivo* for the treatment of autoimmune diseases.

A range of issues have historically limited the use of cellular therapies:

- **Limited therapeutic application:** Given the specialized nature of these prior cellular therapies, they have been designed for specific indications and lack the inherent flexibility to be applied broadly across multiple therapeutic areas.

- **Potentially serious side effects:** Many previous and current cellular therapies can cause serious side effects, including cytokine release syndrome, neurotoxicity and death. These alternative cellular therapies contain a nucleus and retain the ability to expand and differentiate post-injection, potentially raising concern of uncontrolled cell division and transformation.

- **Unpredictable pharmacokinetics and biodistribution:** Current cellular therapies have an uncertain lifetime post-infusion. In some cases, the therapeutic benefits quickly wane. In others, the cells will continue to divide, expand and potentially transform unpredictably over an extended period of time. Additionally, these cellular therapies can extravasate in an untargeted manner into healthy tissues throughout the body, which may result in severe adverse effects.

- **Costly manufacturing and delayed treatment:** Most previous and current cellular therapies are autologous, meaning they must be derived from a patient's own cells to avoid rejection by the immune system. This results in a strictly customized, one-to-one manufacturing process for each individual patient, which is costly and difficult to scale, and involves a complex supply chain that can delay treatment for critically ill patients. Moreover, this approach does not allow for an industrialized effort that can be leveraged to rapidly develop additional product candidates.

Advantages and versatility of our RED PLATFORM and RCTs

Our discoveries and innovations in genetic engineering and cell culture processes allows us to leverage the inherent benefits of RBCs. We believe our RED PLATFORM and RCTs represent a transformative step in the evolution of cellular therapies as they are designed to confer desirable attributes for a next-generation cellular therapy, including the following:

- **Broad therapeutic applications:** We have engineered hundreds of RCTs to have therapeutic potential across many areas, such as rare diseases, cancer, autoimmune diseases, cardiovascular diseases, metabolic diseases and infectious diseases. These RCTs can be designed to express immune-shielded enzymes or other proteins within the cell and

diverse proteins on the cell surface, including combinations of proteins for (1) potent cell-cell interaction with T cells, NK cells or other cells; (2) tissue localization; and (3) induction of immune tolerance.

- **Advantageous tolerability:** Since RCTs lack a nucleus, they possess no genetic material and do not divide following infusion into patients. As a result, we believe our RCT product candidates will pose less risk than those associated with other cellular therapies, which have caused cytokine release syndrome, neurotoxicity and death and carry the potential risk of inducing oncogenicity.

- **Ready-to-use cellular therapies:** O negative donor blood is routinely used for blood transfusions and can be repeatedly transfused into approximately 95% of people. Similarly, RCTs are produced from O negative donor blood stem cells and are therefore allogeneic, ready-to-use cellular therapies that we believe will be tolerated by almost all patients.

- **Defined life in circulation and convenient dosing:** RBCs have a circulating time of approximately 120 days. We expect our RCTs to benefit from this long circulation time, resulting in more consistent pharmacodynamics and convenient dosing regimens thereby improving compliance and real-life efficacy. Furthermore, a single proposed RCT dose will constitute less than 1% of normal red cells in a patient's circulation.

- **Predictable biodistribution:** RBCs normally reside only in the vasculature, the spleen and the liver and do not otherwise extravasate into other healthy tissues. Biodistribution into the spleen allows for RCTs designed to stimulate the immune system to mount an attack against cancer, while biodistribution of RCTs expressing autoimmune disease-causing antigens to specialized cells in the liver can induce tolerance and improve the signs and symptoms of autoimmune diseases. We anticipate that this predictable biodistribution will allow RCTs to trigger on-target desired effects while avoiding off-tissue engagement.

- **Efficient product engine:** Our RED PLATFORM provides a consistent product design and discovery approach where simply changing the added gene or genes that encode the biotherapeutic proteins that confer the intended therapeutic benefit allows us to develop new product candidates targeting different diseases.

- **Scalable and flexible manufacturing:** We manufacture RCTs in bioreactors that we intend to scale to thousands of liters. A single donor will allow us to manufacture up to hundreds to thousands of doses, depending on the therapeutic application. As a result, we expect the cost of goods sold for RCTs to be significantly lower than existing cellular therapies, such as CAR-Ts. We manufacture RCTs using well-characterized and validated lentiviral vectors. Cellular engineering approaches, such as viral and non-viral transduction systems and mRNA delivery, may also be applied to RCTs which may provide additional product benefits and cost advantages.

Our strategy

Our vision is to pioneer the creation of life-changing or life-saving and ready-to-use RCTs for patients with severe diseases. To achieve our vision, we are executing a strategy with the following key elements:

Establish RCTs as a new class of cellular medicines, demonstrating their potential across three initial product categories: rare diseases, cancer and autoimmune diseases. We apply a rigorous and capital-efficient approach to prioritize our product candidate pipeline, focusing on unmet need, feasibility, speed to proof-of-concept, easy-to-measure validated endpoints and commercial potential. In March 2019, the FDA cleared our IND for RTX-134 for the treatment of PKU. We expect to begin enrolling patients for the Phase 1b clinical trial of RTX-134 during the second quarter of 2019, with initial data expected during the second half of 2019. In total, we plan to file a total of four to five INDs by the end of 2020, with additional filings thereafter.

Efficiently advance multiple additional RCTs as product categories are validated following positive early proof-of-concept. We expect that early clinical success of our initial RCT product candidates could translate to other programs within the product category, validating our approach and enabling a rapid and efficient expansion of our rare disease, cancer and autoimmune disease product categories. For example, positive early clinical proof-of-concept for

RTX-134 will validate the benefits of our approach for treating rare enzyme deficiency diseases using cellular shielding of potent enzymes and support our ability to successfully develop additional RCTs within this product category.

Pursue accelerated paths to marketing authorization. We are pursuing indications with high unmet medical needs that may allow us to pursue accelerated paths to product registration, such as breakthrough therapy designation or RMAT designation by the FDA. Similarly, we expect to pursue accelerated routes to marketing authorization in Europe and other regions.

Build a leading, fully integrated cellular therapy company. We are discovering, developing, manufacturing and may commercialize RCT products within certain product categories. Following potential approval of multiple RCT products in a particular category, we may leverage a dedicated commercial infrastructure to deliver our therapies to patients.

Further strengthen our position as the pioneer of RCTs through continuous platform expansion and improvement. Our proprietary RED PLATFORM allows us to rapidly identify new product candidates and includes a universal manufacturing process for all RCT product candidates. We will continue to invest in enhancing our platform and deepening our expertise in stem cell and red cell biology and optimizing the pharmacology of RCTs with the goal of delivering new therapies targeting additional indications. We plan to leverage our first-mover advantage in manufacturing RCTs as we scale-up our proprietary manufacturing platform. To fully support later-stage clinical development and commercial launch, we plan to ensure control over our supply chain. As an initial investment in this strategy, we purchased a manufacturing facility and are in the process of renovating it to provide multi-suite manufacturing capabilities.

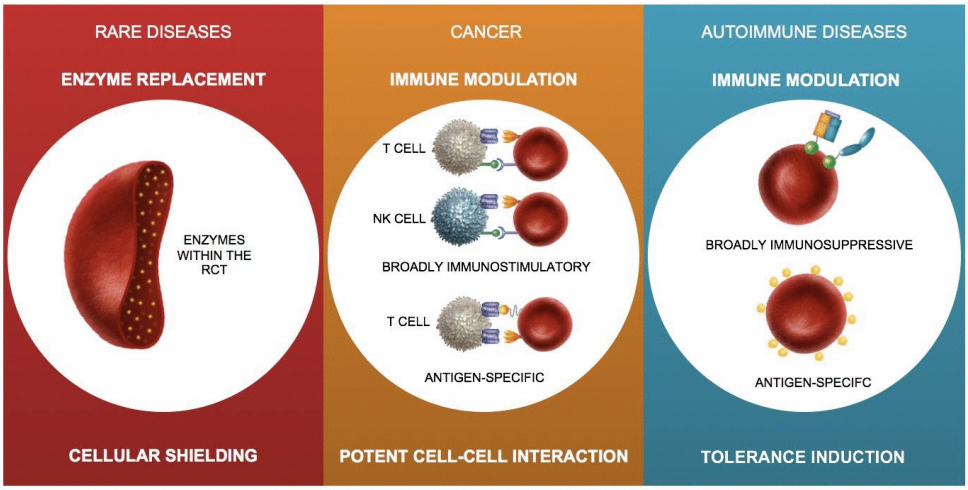
Expand patient access to RCTs through strategic partnerships. Given the breadth of the therapeutic opportunity for RCTs, we believe entering into select strategic partnerships in a subset of therapeutic areas may provide an attractive avenue for expanding patient access to RCTs. The global reach and operational expertise within certain pharmaceutical companies may complement our growing organization in areas such as clinical operations and commercialization.

Maintain a strong culture, continuously attract new talent and build the world's leading center for red cell biology research and engineering. We are located in one of the world's leading hubs for biopharmaceutical innovation, which enables us access to world-class talent, leading academic investigators and key opinion leaders. We have leveraged our location to attract scientific talent and experienced, innovative leaders and have built a strong culture that is committed to delivering on our vision. In addition, we have assembled a network of scientific advisors with deep expertise in red cell biology, process development and manufacturing as well as clinical experience across the therapeutic areas that we are initially targeting. We will continue to build a team of employees, advisors and collaborators with experience in the discovery, development, manufacture and commercialization of cellular therapies.

Initial therapeutic areas of focus

Based upon the totality of scientific and preclinical work to date, we believe that RCTs have broad potential therapeutic applications. Our initial focus will be advancing RCT product candidates with unique benefits for patients with rare diseases, cancer and autoimmune diseases based on three modalities — cellular shielding, potent cell-cell interaction and tolerance induction.

Select RCT Modalities to Treat Rare Diseases, Cancer and Autoimmune Diseases



Rare diseases

We believe that RCTs may be used to treat certain rare diseases caused by a single genetic defect that results in the inactivation of a critical metabolic enzyme or bioactive protein. Manufacturing the missing protein or enzyme and administering it to the patient may potentially correct this deficiency, but unfortunately many of these proteins or enzymes are highly immunogenic or poorly tolerated by patients, thereby limiting or, in some cases, preventing their therapeutic use. While biopharmaceutical companies are developing gene therapies for the treatment for several diseases caused by single genetic defects, this approach has historically been associated with unpredictable outcomes, including inconsistent efficacy and the potential for toxicity. In contrast, RCTs may provide the following benefits to patients suffering from rare diseases:

- **Highly active therapy through cellular shielding:** RCT product candidates engineered to express enzymes and other proteins within the cell, including poorly tolerated non-human enzymes, effectively hide these proteins from the immune system, thereby shielding them from being neutralized or causing severe adverse effects, such as anaphylaxis. We expect these cellular shielding RCT product candidates will provide well-tolerated and predictable therapeutic benefits, which may enable their chronic use and adoption as the preferred treatment option for a number of rare diseases.

- **Convenient dosing regimen:** Based on RBCs' approximate circulation time of 120 days, we expect our RCT product candidates will have substantially longer half-lives in patients compared to current treatments, many of which require a daily or weekly treatment regimen. This expected extended *in vivo* half-life would allow for a more convenient dosing regimen of monthly to quarterly infusions, which may drive higher compliance with therapy and improve real-life efficacy.

Our initial RCT product candidates in rare diseases include RTX-134 for the treatment of PKU. In March 2019, the FDA cleared our IND for RTX-134 for the treatment of PKU. We expect to begin enrolling patients for the Phase 1b clinical trial of RTX-134 during the second quarter of 2019, with initial data expected during the second half of 2019. We anticipate RTX-134 will be followed by several additional programs including RTX-Uricase for the treatment of chronic refractory gout and RTX-CBS for the treatment of homocystinuria.

Cancer

We believe that RCTs will have broad therapeutic applicability across a range of both solid and hematological cancers. Beyond standard chemotherapy and radiotherapy treatments that have historically been the mainstay of care, a growing number of small molecule, antibody, nanoparticle and cellular therapies are now being applied to the treatment of cancer. While extraordinary lifespan and quality of life gains have been made, many treatments fail to provide benefit to patients or the disease relapses over time due to cellular escape mechanisms that make specific tumors unresponsive to these treatments. RCTs may provide the following benefits to cancer patients:

- **Immune activation via potent cell-cell interaction:** Our RCT product candidates have been engineered to broadly stimulate the adaptive and innate immune systems through T cell activation and NK cell activation, thereby stimulating these cells to attack and kill tumors. We have observed *in vitro* and *in vivo* that our RCT product candidates bind and activate multiple existing and emerging immuno-oncology targets. Due to both the natural presentation and the high copy number of the expressed protein, which results in strong binding to cellular receptors, along with the ability to co-express multiple proteins on the surface of each RCT, surface-engineered RCTs may either (i) elicit potent immunostimulatory effects in immunogenic tumors characterized by higher mutation rates, T cell infiltration or checkpoint protein expression, or (ii) enable non-immunogenic tumors to become immunogenic and then drive immunostimulatory effects.
- **Antigen specific immune activation via cell surface antigen presenting:** Other RCT product candidates of ours have been engineered to express a tumor associated antigen, a co-stimulatory signal and a cytokine at the same time on the same cell. This represents a recapitulation of normal human immune biology and results in highly selective tumor cell killing and the generation and maintenance of T-cell memory.
- **Tumor starvation:** We have developed RCT product candidates that express enzymes designed to deplete essential amino acids from the tumor microenvironment. This approach can starve a fast-growing tumor of a metabolite that is essential for its growth and proliferation. This approach has shown potential in certain pediatric cancers although enzymes used for this approach are often highly immunogenic and poorly tolerated. We believe that shielding these enzymes from the immune system may reduce immunogenic side effects, prolong therapeutic exposure and thus lead to a more efficacious therapy.
- **Tumor targeting and killing:** Our RCT product candidates have been generated with high copy numbers of tumor-binding and tumor-killing proteins on their surface. By virtue of the high copy number and presentation of these proteins via membrane attachment, we believe that these RCT product candidates will demonstrate high target binding strength on the surface of cancer cells to drive potent anti-tumor responses. Selectively engaging immune cells in the vasculature may limit the on-target/off-tissue side effects seen with other immuno-oncology therapies.

Our first RCT product candidate in cancer is RTX-240 (formerly RTX-212), which we expect to initially study in patients whose disease has progressed on checkpoint inhibitor therapy across a range of solid tumor types and in patients with acute myeloid leukemia following hematopoietic stem cell transplant. Additionally, we are advancing our second product, RTX-224, in a similar setting, but with the added benefit of potentially addressing patient sub-populations with non-immunogenic tumors. Finally, we are developing a number of RCTs that function as artificial antigen-presenting cells. Our initial focus is for the treatment of HPV16+ expressing tumors, including head and neck and cervical cancer, among others. We plan to follow this with a range programs that could target viral antigens, cancer/testis, or CT, antigens and neoantigens.

Autoimmune diseases

Our RCT product candidates have shown potential in preclinical studies for the treatment of autoimmune diseases. Available therapies for autoimmune diseases have significant limitations because these therapies are required to be administered on a chronic, lifelong basis. Many treatments fail to provide adequate benefit to patients, and many patients' diseases will eventually progress despite continued therapy. Furthermore, these existing treatments are associated with side effects that include opportunistic infections, lymphoma and in some cases severe and even fatal infusion reactions. We believe RCTs can be designed to more specifically modulate complex counter-regulatory immune responses and enable greater efficacy with lower toxicity, potentially providing treatments for a number of diseases with

high unmet need. Specifically, RCTs may provide the following benefits to patients suffering from autoimmune diseases:

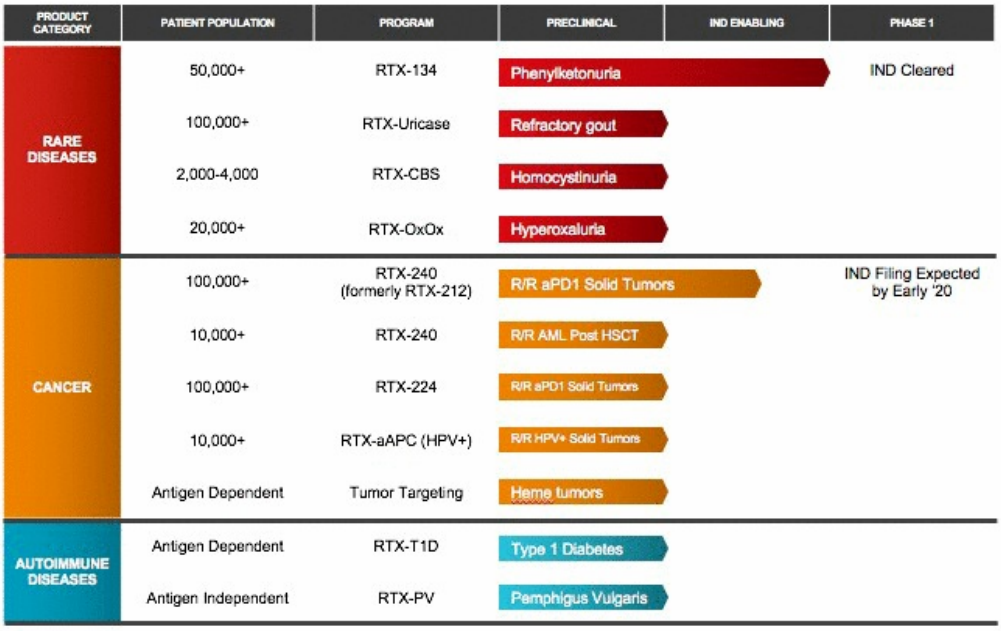
- **Induction of peripheral tolerance:** We believe the processing of RCTs that express autoimmune disease-causing antigens by specialized cells in the liver can induce tolerance and improve the signs and symptoms of autoimmune diseases. Our preclinical data suggests that RBCs are capable of inducing peripheral tolerance to RBC-bound antigens, which is the ability to prevent these antigens from triggering dangerous responses to the body's own tissues. We have observed the feasibility of this approach in preclinical studies in models of neurodegeneration and diabetes and believe that many proteins presented on RCTs should benefit from this tolerance induction. We believe our antigen-specific autoimmune RCT product candidates have the potential to be curative therapies for antigen-induced autoimmune diseases, including Type 1 diabetes.
- **Cytokine neutralization:** The high copy number and thereby high local density of a binding protein on the surface of an RCT enables efficient sequestration and neutralization of soluble targets in circulation. This may also limit off-target effects by confining the binding protein to the vasculature through expression on the RCT cell surface. In preclinical studies, we have observed the ability of RCTs to bind cytokines and foreign proteins with high affinity and thereby neutralize their function. For example, we have observed the ability of an RCT that expresses an anti-TNF-alpha protein on its cell surface, to neutralize lethal doses of TNF-alpha in preclinical studies.
- **Antibody clearance:** High affinity capture of antibodies on RCTs could allow for effective neutralization and clearance of pathological antibodies for the potential treatment of autoimmune diseases, such as idiopathic thrombocytopenia. Clearance may be enhanced when surface binding is complemented with a surface-expressed protease, resulting in the destruction of the pathological antibody. We have observed the ability of RCTs to bind to circulating antibodies both *in vitro* and *in vivo*. We have also co-expressed antibody binders and proteases on the surface of RCTs and observed that they are active.
- **Targeting and inhibiting immune cells:** We have engineered RCTs to induce the activation of certain immune regulatory cells, which in turn alter the body's general immune repertoire and restore the system to a tolerogenic state.

We are currently assessing these RCT product candidates and expect to select our first clinical candidate for treatment of autoimmune diseases in 2019.

Our product candidate pipeline

We are building a broad and diverse pipeline of RCT product candidates in rare diseases, cancer and autoimmune diseases. In March 2019, the FDA cleared our IND for RTX-134 for the treatment of PKU. We expect to begin enrolling patients for the Phase 1b clinical trial of RTX-134 during the second quarter of 2019, with initial data expected during the second half of 2019. We expect to file a total of four to five INDs by the end of 2020, with additional filings thereafter. Our first product candidates were selected based on: potential to address unmet medical needs; feasibility as determined by our preclinical research and development efforts; potential to rapidly achieve proof-of-concept based on easy-to-measure validated regulatory endpoints; and significant commercial potential.

An overview of our programs and their status is illustrated below:



Definitions: CBS—cystathionine beta synthase; OxOx—oxalate oxidase; αPD1—patients progressed on or refractory to anti-programmed death receptor 1 monoclonal antibody; R/R AML—acute myeloid leukemia; HSCT—hematopoietic stem cell transplant; HPV+—Human papilloma virus positive; APC—antigen presenting cell

Rare diseases

Our initial rare disease programs target enzyme deficiencies with limited treatment options. Our RED PLATFORM allows us to explore a broader range of human, non-human, engineered and combinations of enzymes with higher activity than those available to companies developing native or pegylated products. Clinical trials in rare disease indications are of a relatively short duration, of modest size and employ validated biomarkers that can be used to highlight initial efficacy and support product approval.

RTX-134 for treatment of phenylketonuria

Indication / opportunity

PKU is caused by a deficiency of functional phenylalanine hydroxylase, or PAH, which is the enzyme that breaks down dietary phenylalanine, or Phe. Phe is an essential amino acid found in many foods including milk, eggs, meat and soybeans. Patients with PKU are unable to break down Phe and the resulting high levels of Phe can cause motor dysfunction, psychiatric disorders and irreversible brain damage.

Newborn screening programs, which were implemented in the 1960s and 1970s, are used throughout the developed world to identify children with PKU and, as a result, virtually all patients with PKU under the age of 40 have been diagnosed at birth. It has been estimated that the incidence of PKU in the United States is one in 12,707, which translates to approximately 300 cases per year with an overall prevalence of 15,000. It has also been estimated that the prevalence

of PKU in the E.U. is 25,000. Worldwide, the estimated prevalence is more than 50,000. The clinical presentation of PKU ranges from mild to severe, with blood Phe levels measured to determine disease severity. In Classic PKU, Phe levels are 1,200 μmol/L or greater; in Moderate PKU, Phe levels range from 600 to 1,200 μmol/L; and in Mild PKU, Phe levels are below 600 μmol/L.

Patients with Classic PKU comprise approximately 40% of all PKU patients in the United States, are at the greatest health risk and are the most difficult to treat. Typical symptoms in children with Classic PKU include seizures, behavioral problems and delayed development. Without proper treatment, progressive motor dysfunction is inevitable. Studies have indicated that for each 300 μmol/L rise in average Phe for those aged five to eight years, patient's IQ fell by four to six points. Adults with Classic PKU exhibit a range of symptoms, including deterioration in executive function (such as language, memory, learning), attention deficit issues, depression, anxiety, impaired affect and autistic features and Parkinsonian-like tremors. These manifestations of the disease result in a profoundly impaired quality of life and an inability to comply with treatment, potentially resulting in further deterioration of executive function.

Patients with Moderate PKU represent approximately 20% of all PKU patients in the United States. They can often manage their disease by adhering to a tightly restricted, protein free diet. However, if the disease is not managed diligently, these patients remain at risk of intellectual disability and are likely to exhibit signs of neuropsychological disturbances. Patients with Mild PKU, who represent the remaining 40% of all U.S. PKU patients, are at a lower risk for impairments in executive function but may still benefit from treatment if Phe levels are above 120 μmol/L.

Our initial target patient population for RTX-134 will be patients with Phe levels greater than or equal to 600 μ mol/L.

Limitations of current therapies

Treatment in the first decade of life is essential in realizing optimal clinical outcomes for PKU patients. The current mainstay of therapy for PKU is an extreme restriction of dietary Phe and requires that patients purchase expensive and unpalatable specially formulated medical foods. Since breast milk contains Phe, pediatric patients are started on a low Phe regimen at birth and plasma levels are monitored weekly until age five. In general, with great effort, parents are able to manage the diet of the youngest children with PKU and most are well controlled.

Target Phe levels in adolescence and adulthood are less clear but it is generally accepted in the United States that patients with Phe levels below 600 μmol/L are at lower risk of cognitive impairment over time. Guidelines suggest that dietary restrictions should continue indefinitely, however compliance tends to wane as patients age and enter school. Adolescents with PKU may find it challenging to comply with the extreme dietary restrictions that are required to control their Phe levels, and since they are undergoing active neural maturation they are particularly at risk of cognitive impairment. Only a minority of adult patients are well controlled based upon diet alone. Once dietary compliance falters, the odds that a patient will return to treatment becomes less likely over time. In addition, the long-term outcome of extreme protein restriction in patients is not clear and there are clinical studies ongoing to assess the impact on bone and renal health.

Sapropterin dihydrochloride, or sapropterin, was the first therapy approved in the United States to treat PKU. Sapropterin is an oral synthetic version of BH4, a cofactor that is required for PAH activity. Administering this cofactor can be helpful for patients with existing but ineffective PAH. Clinical data, however, suggests that sapropterin is not fully effective in lowering high serum levels of Phe back to normal levels and it must be used in conjunction with a low Phe diet. Sapropterin is used in fewer than 15% of PKU patients, in part due to lack of efficacy in patients with more severe Classic PKU.

Phenylalanine ammonia lyase, or PAL, is a naturally occurring enzyme that is primarily found in some plants and fungi and which converts Phe to ammonia and trans-cinnamic acid, or TCA. TCA is subsequently converted to hippuric acid in the liver and cleared from the body through urinary excretion. Although administration of PAL has been shown to reduce Phe levels in preclinical studies and clinical trials of PKU patients, it has also been found to be highly immunogenic.

Pegvaliase, a pegylated version of PAL, was approved in May 2018 by the FDA to reduce blood phenylalanine concentrations in adult patients with phenylketonuria who have uncontrolled blood phenylalanine concentrations greater than 600 micromol per liter on existing management. However, in its registrational trials, neutralizing antibodies were detected in 249 out of 284, or 88%, of the patients and many of the patients that participated in the first phase (PRISM 1) failed to reach the target of a 20% reduction in Phe, which was the entry criteria for the placebo-controlled phase (PRISM 2). In addition, pegvaliase caused hypersensitivity reactions and anaphylaxis, which necessitated an extended tolerization schedule resulting in months of delay to reach a therapeutic dose. The drug's black box warning label indicates that the first injection should be administered under the supervision of a healthcare provider equipped to manage anaphylaxis, and then should be administered as a daily subcutaneous injection, which makes compliance with the treatment regimen difficult, particularly as patients go through this extended tolerization period. Physicians are instructed, per the black box warning label, to prescribe auto-injectable epinephrine, and patients are instructed to carry one at all times while on therapy.

Pegvaliase is priced at $488 per 20 mg/ml syringe wholesale acquisition cost, and BioMarin Pharmaceutical, Inc. expects that, when taking compliance and discounts into account, the cost per patient per year is expected to be $192,000. Even in the absence of pegvaliase treatment, the cost of care for PKU patients can add up to more than $100,000 per year, which can include costs for medical foods and current therapies. Additional inpatient mental health and residential medical facility care for patients can cost between $60,000 and $200,000 per year depending on the patient's level of intellectual and functional disability. These are only the most significant direct costs and do not include the indirect economic impact of an impaired ability to work or maintain meaningful employment.

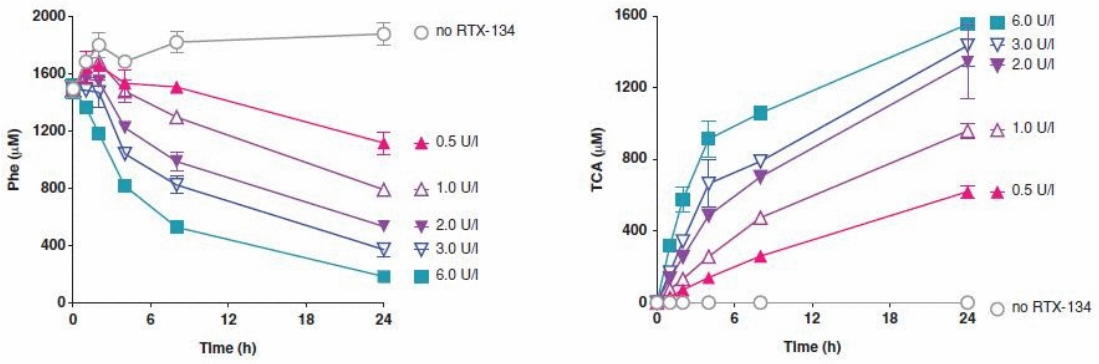
Overall, treatment options for the majority of Classic and Moderate PKU patients are limited. We believe that an RCT product candidate that expresses PAL has the potential to overcome the limitations of existing therapies and offer relief to patients suffering from PKU.

Product candidate description and preclinical data

RTX-134 is an RCT product candidate that we have genetically engineered to express PAL in the cytosol of the RCT. We expect RTX-134 will reduce Phe to clinically meaningful levels through infrequent, low volume intravenous infusions. We plan to apply for orphan drug designation for RTX-134.

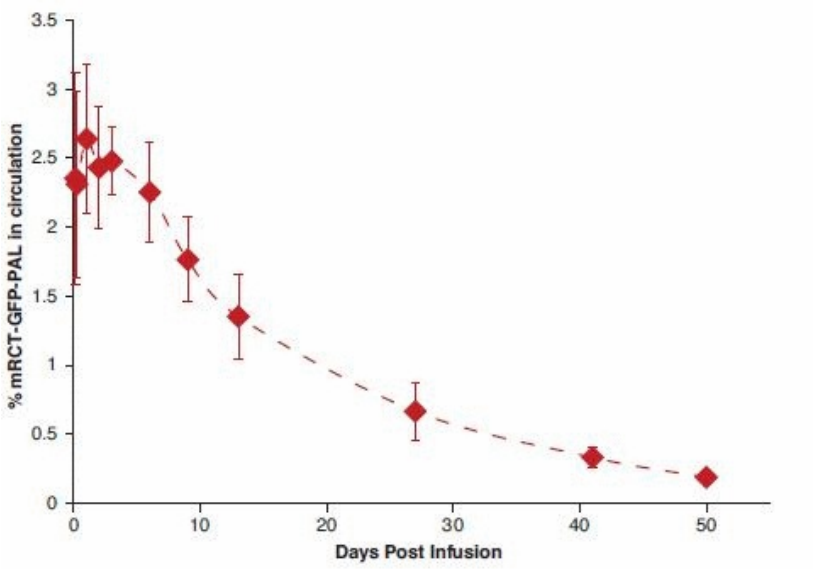
In preclinical studies, we have observed that PAL is highly active when expressed in the cytosol of RTX-134 as measured both by reduction in Phe and concomitant generation of TCA. We have also observed that Phe uptake into RTX-134 is not rate limiting for its activity.

***In Vitro* Reduction of High Levels of Phe and Concomitant Generation of TCA by RTX-134 in Human Serum**



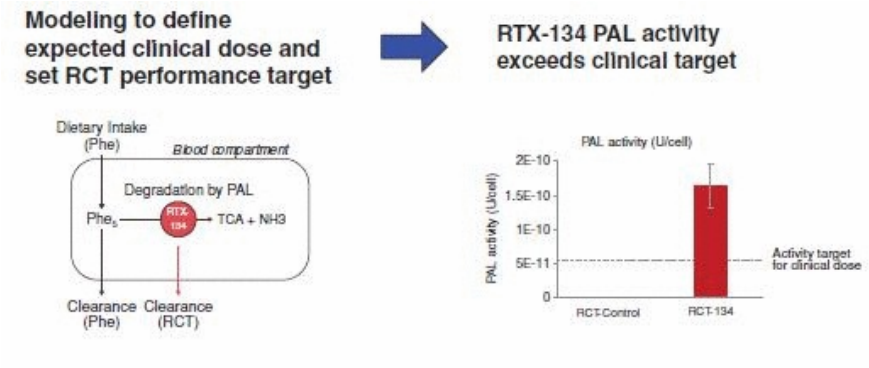
In preclinical mouse studies, we observed that PAL expressing murine RCTs, or mRCT-GFP-PAL, have a circulation time of approximately 50 days, which is equivalent to the normal circulating time of mouse RBCs. Based upon this finding, we expect RTX-134 to have an approximate circulating time of up to 120 days in PKU patients, the normal circulating time of human RBCs.

Circulation Time of mRCT-GFP-PAL



Based on available clinical data from PKU patients and our preclinical data, we have developed a pharmacodynamic model for RTX-134 to project the RTX-134 starting dose in the first clinical trial in PKU patients.

Pharmacodynamic Model Informs PAL Activity Target for RTX-134



Clinical development

In March 2019, we announced that the FDA cleared our IND for RTX-134 for the treatment of PKU. We expect to begin enrolling patients for the Phase 1b clinical trial of RTX-134 during the second quarter of 2019, with initial data expected during the second half of 2019. The clinical objectives associated with our initial Phase 1b trial of RTX-134 are preliminary safety; longevity of cells in circulation; production of trans-cinnamic acid, a biomarker of RTX-134's mechanism of action; and preliminary dose and schedule.

Following FDA review of the data from the Phase 1b trial, we plan to investigate multi-dose administration of RTX-134 to further evaluate safety and magnitude of Phe reduction which is a measure of efficacy in PKU trials. Assuming favorable results from the planned multi-dose administration phase of the trial, we expect to advance RTX-134 to a registrational trial and to begin a pediatric trial.

RTX-Uricase for treatment of chronic refractory gout

Indication / opportunity

Gout is a metabolic and inflammatory disease often affecting middle-aged to elderly men and postmenopausal women. After years of repetitive attacks, patients develop chronic refractory gout, which is characterized by the buildup of tophi, or deposits of uric acid crystals in the joints, kidney and heart. Tophi can lead to the development of chronic arthritis and an increased risk of developing kidney stones, chronic renal insufficiency and cardiovascular disease. Once patients reach this stage, they generally suffer multiple attacks every year.

The prevalence of gout increases with age and risk factors include insulin resistance, obesity, and a diet rich in meat and seafood. The number of patients diagnosed with gout in the United States is estimated to be approximately eight million and is increasing with population growth. In Europe, prevalence is equal or close to that in the United States at this time. Approximately 50,000 to 60,000 gout patients in the United States per year fail all therapy and are considered chronic refractory.

Limitations of current therapies

Patients who experience at least two attacks per year or present with tophi are considered candidates for uric acid-lowering therapy. Three classes of therapies are currently approved for decreasing uric acid levels: xanthine oxidase inhibitors, uricosuric agents and uricase agents.

The first-line standard of care for gout is xanthine oxidase inhibition, which blocks uric acid synthesis, and is an effective treatment option for many. For patients who require more control or who are contraindicated, the uricosuric agent, lesinurad, may be prescribed. Lesinurad is an oral inhibitor of URAT1, which is the transporter that mediates reuptake of uric acid from the proximal tubules of the kidney and drives renal elimination of uric acid. Lesinurad carries a black box warning associated with renal toxicity and is contraindicated in patients with renal impairment.

Chronic refractory patients are candidates for pegloticase, which converts uric acid into allantoin, which is then excreted via the kidneys. Pegloticase is the only currently approved uricase agent available for the treatment of chronic refractory gout. Pegloticase, while generally considered effective, has several shortcomings. It carries a black box warning for anaphylaxis and there have been serious cardiovascular events associated with pegloticase. Furthermore, its administration is inconvenient with patients having to undergo a four-hour premedication/infusion process once every two weeks.

The economic burden of chronic refractory gout is driven by a combination of emergency room visits, bedridden days and recurring loss of economic productivity. Over time, the progression of the disease may result in long-term disability. Beyond these costs, patients with recurring attacks and higher serum uric acid levels also suffer high rates of hypertension, renal impairment, chronic kidney disease, dyslipidemia and ischemic heart disease.

Overall, treatment options for the majority of the chronic refractory gout patients are limited. We believe that an RCT product candidate that expresses uricase has the potential to overcome the limitations of existing therapies and offer relief from debilitating pain to the tens of thousands of patients suffering from chronic refractory gout. Based on the expected tolerability profile, RTX-Uricase may also have applications in a broader chronic gout population as prior lines of therapy carry black box safety warnings.

Product candidate description and preclinical data

RTX-Uricase is an RCT product candidate that we have genetically engineered to express hundreds of thousands of copies of uricase along with a uric acid transporter that ensures optimal uptake of uric acid into the cell. We expect that RTX-Uricase will augment a patient's ability to clear uric acid, meaningfully reduce uric acid levels in the blood, and reduce the frequency of painful attacks and number of tophi. We also believe that the shielding of uricase in our RCT will avoid the safety concerns associated with the administration of pegloticase. We anticipate that RTX-Uricase will require monthly or less frequent dosing with low volume intravenous infusions. We plan to file for orphan drug designation given the small, well-defined patient population and the unmet need.

Similar to the clinical candidate development approach that we used for RTX-134, we have developed a pharmacodynamic model for RTX-Uricase and have determined the target uricase activity needed to achieve clinically meaningful reductions in uric acid. As part of our lead development and optimization process, we have demonstrated that RCTs expressing uricase and a transporter meet the targeted expression and activity levels and have demonstrated co-expression of uricase and a transporter for RTX-Uricase.

Clinical development

We plan to study RTX-Uricase in patients with chronic refractory gout to determine the safety profile, appropriate RTX-Uricase dose and dosing interval needed to achieve serum uric acid of less than 6 mg/dL. At uric acid levels below 6 mg/dL, uric acid crystals do not form and crystals already formed begin to dissolve. This target goal for demonstrating efficacy in chronic treatment refractory gout patients has been accepted by the FDA and the EMA and was the basis for approval of pegloticase.

RTX-CBS for treatment of homocystinuria

Indication / opportunity

Homocystinuria refers to a group of enzyme deficiency disorders that result in elevated levels of circulating homocysteine, or Hcy, and its metabolites. The majority of homocystinuria patients suffer mutations of a gene that regulates the production of the enzyme known as cystathionine beta-synthase, or CBS, which is required for the conversion of Hcy to cystathionine.

Homocysteine is a highly reactive amino acid that can cause lipid peroxidation and DNA damage, cellular metabolic disruption, programmed cell death and immune activation, which all contribute to atherogenesis, or the formation of abnormal plaques in the inner lining of blood vessels. Elevated levels of homocysteine result in a wide range of deforming and debilitating symptoms. By age three, failure to thrive is generally apparent and partial dislocation of the lens of the eyes and severe myopia are common. Without treatment, children may suffer from progressive and severe neurodegeneration. In addition, many of these children will develop psychiatric disturbances and experience seizures. A failure to effectively treat patients over time can also result in aberrant musculoskeletal development, including Marfanoid features, characterized by abnormally long limbs and digits and scoliosis, or spinal curvature. Patients with homocystinuria suffer from extreme hypertension and are at an elevated risk for the development of thromboembolisms. If untreated, approximately 50% of patients will have a thromboembolic event and the overall mortality rate is approximately 20% by age 30.

The signs and symptoms of homocystinuria typically develop within the first year of life, but some mildly affected patients may not develop symptoms until later in life, particularly because this is a progressive disorder. Patient population estimates range widely, but the National Organization for Rare Disorders suggests a worldwide prevalence of 1:344,000, which when applied to the combined U.S. and E.U. population of 830 million would suggest an initial

treatment market of approximately 2,400 diagnosed patients in these regions. However, this is potentially an underrepresentation of the true population size as the literature suggests that current newborn screening tests may not be adequately sensitive or specific. This suggestion is further reinforced by the fact that patients may present with thromboembolism later in life, without a prior diagnosis. Finally, studies based on genotyping rather than clinical diagnosis conducted in Europe suggest a much higher prevalence of potentially asymptomatic patients. The burden and cost of care for homocystinuria is high as the major clinical manifestations of the disease include mental retardation, dislocation of the optic lens, skeletal deformity and potentially fatal thromboembolic crises.

Limitations of current therapies

The general therapeutic goal for homocystinuria is to reduce serum and cellular Hcy accumulation and thus limit the development of existing symptoms and prevent the onset of new symptoms. Early diagnosis, treatment and aggressive diet restriction have been shown to slow the progression of disease as well as to reverse some of the symptoms. Treatment practice varies widely and compliance with diet drops with age. High-dose pyridoxine, or vitamin B6, is a treatment capable of relieving some clinical symptoms of disease for approximately half of all homocystinuria patients. Even for those for whom it is effective, though, it carries the significant limitations of requiring a moderately restrictive diet and the risk of overdosing. Meanwhile, patients who do not respond to vitamin B6 treatment remain subjected to a stringent protein restricted diet along with a methionine-free amino acid formulation supplement, which they are often not able to maintain.

An oral betaine anhydrous solution is the only approved drug for homocystinuria. Physicians' use of betaine varies widely in practice and there is preclinical data to suggest that patients become non-responsive to betaine supplementation resulting in waning efficacy over time.

Overall, treatment options for most patients with homocystinuria are limited. We believe that an RCT product candidate that expresses CBS has the potential to overcome the limitations of existing therapies and offer relief to patients diagnosed with homocystinuria and ultimately reduce the risk of thromboembolisms and cardiac events in those patients that present without symptoms.

Product candidate description and review of preclinical data

RTX-CBS is an RCT product candidate that we have genetically engineered to express hundreds of thousands of copies of CBS in the cytosol of the cell. We expect RTX-CBS will replace the patient's missing or ineffective enzymes and rapidly drop total plasma homocysteine, or tHcy, levels to clinically meaningful targets through infrequent, low volume intravenous infusions.

Similar to RTX-134 and RTX-Uricase, we have established a pharmacodynamic model to determine the target CBS activity required for clinical activity and to project clinical dose levels and frequency. Enzyme expression refinement in RTX-CBS is still ongoing and we are characterizing the transport of Hcy and serine into RTX-CBS and secretion of cystathionine out of the cell to determine whether or not co-expression of a transporter may be required.

Clinical development

Our target indication for RTX-CBS will be the treatment of patients suffering from symptomatic homocystinuria who are unresponsive to vitamin B6 therapy. Pending confirmation by the FDA, we expect that reduction in plasma tHcy levels to be below 50 μM will be an acceptable primary endpoint for our clinical trials. We plan to evaluate RTX-CBS in patients with symptomatic homocystinuria based on genetic confirmation of CBS mutation and plasma tHcy equal or greater than 100 μM. In such evaluation, our goal is to determine the safety profile, appropriate dose and dosing interval of RTX-CBS necessary to maintain plasma tHcy below clinical target levels. As the disease is primarily diagnosed in pediatric patients and can be lethal, we will explore the potential for obtaining a rare pediatric disease priority review voucher from the FDA.

Rare diseases discovery research

Our RED PLATFORM has generated RCT product candidates that shield immunogenic enzymes and express transporters on their surface. As a result, we believe that we can design RCTs to address many rare diseases where pathogenic metabolites build up. We are using the same RCT product candidate development approach as applied for RTX-134, RTX-Uricase and RTX-CBS to develop a portfolio of RCTs for treatment of a range of rare diseases. One example is RTX-OxOx, which expresses oxalate oxidase for the treatment of second-line hyperoxaluria, a condition characterized by recurrent kidney and bladder stones, which can result in end stage renal disease in severe cases.

Cancer

We believe that RCTs will have broad therapeutic applicability across a range of both solid and hematological cancers and are developing a pipeline of RCTs that target T cells, NK cells, dendritic cells, tumor cells, or combinations thereof.

Our lead product candidates for the treatment of cancer are RTX-240 (formerly RTX-212) and RTX-224. RTX-240 is a RCT that co-expresses both 4-1BBL and IL-15TP, a fusion of IL-15 and IL-15 receptor alpha, which synergizes with 4-1BBL to activate and expand both T cells and NK cells. We expect to file an IND for RTX-240 by early 2020. RTX-224 is a combination RCT expressing both 4-1BBL and IL-12. IL-12 drives the proliferation of CD8+ and CD4+ T cells, as well as NK cells. In addition, the IL-12 cytokine is known to drive antigen presentation and inhibit angiogenesis. We believe that both product candidates provide potentially transformative and differentiated approaches to treating patients with solid or hematological tumors whose disease responds to immunotherapies, including CAR-T, as well as tumors that are or have become resistant or refractory to immunotherapies, including checkpoint inhibitors. We expect to initially study RTX-240 in patients whose disease has progressed on checkpoint inhibitor therapy across a range of solid tumor types and in patients with acute myeloid leukemia following a hematopoietic stem cell transplant. We expect to study RTX-224 in patients with a range of both immunologically active and immunologically inactive solid tumors.

Additionally, we are advancing RCTs that function as artificial antigen presenting cells, or RTX-aAPCs. Our initial focus is on displaying tumor antigens fused to major histocompatibility complex class I, or MHC I, on the surface of RCTs that also express a costimulatory signal, such as 4-1BBL and a cytokine such as IL-12 or IL-15. We expect to study one or more of these RTX-aAPCs in patients with tumors that express these antigens. Our lead aAPC program targets HPV+ tumors, of which head and neck and cervical cancer are the most common. Treatment options for HPV16+ refractory and relapsing disease, including head and neck, and cervical cancer are limited, and our goal is to be able to offer patients a potent and highly specific immune stimulation.

We are also exploring tumor-targeted RCTs that co-express 4-1BBL and single-chain variable fragments, or scFvs, that bind to tumor antigens. We expect tumor-targeted RTX-4-1BBL to provide a potent, selective and potentially safe treatment for hematological tumors either as a monotherapy or in combination with existing adoptive cell therapies or checkpoint inhibitors.

RTX-240 and RTX-224

Each of RTX-240 and RTX-224 have been engineered to act as combination therapies that stimulate both the adaptive and innate arms of the immune system. We believe this synergistic activity has the potential to provide the following therapeutic benefits:

- ***Improved anti-tumor activity through broad and sustained activation of the immune system:*** Both RTX-240 and RTX-224 drive robust stimulation of both T cells and NK cells as 4-1BBL and the cytokines (IL-15TP or IL-12) are simultaneously presented in high copy numbers to these immune cells, thereby simulating a potent adaptive and innate immune response. We expect this to result in improved response rates, progression free survival, or PFS, and overall survival, either as monotherapy or in combination with existing immunomodulatory therapies, such as checkpoint inhibitors and CAR-T.

- ***Prevention of resistance to immunotherapy:*** T cells recognize and kill cancer cells via MHC I. A recognized mechanism of tumor resistance to checkpoint inhibitors is loss of MHC I expression, which makes the cancer less

susceptible to T cell mediated killing. However, loss of MHC I makes the tumor susceptible to recognition and killing by the NK cells that have been expanded and activated by RTX-240. We, therefore, expect that RTX-240 used either alone or in combination with immunotherapies will prevent the emergence of resistance to T cell mediated killing through potent NK cell activation and expansion.

- ***Efficacious in tumors that are resistant or refractory to immunotherapy:*** We expect RTX-240 to provide therapeutic benefits to patients whose disease has progressed on checkpoint inhibitors. In these patients, we expect that RTX-240 will promote tumor killing through NK cell and T cell activation and expansion. The addition of IL-12 to 4-1BBL, in the case of RTX-224, is expected to drive the upregulation of T cell and NK cell activity, as well as angiogenesis inhibition and antigen presentation. The latter is important when addressing tumors that do not respond to existing immunotherapies.

- ***Tolerability:*** We expect RTX-240 and RTX-224 to be confined to the vasculature, spleen and liver and, in some cases of leaky neo-vasculature, the tumor itself. We believe this makes these product candidates less likely to trigger on-target/off-tissue effects. Direct systemic administration of cytokines, including IL-15, IL-12 and other interleukins, is currently limited by safety and tolerability concerns, which result in a narrower therapeutic window.

RTX-240 and RTX-224 for the treatment of solid tumors

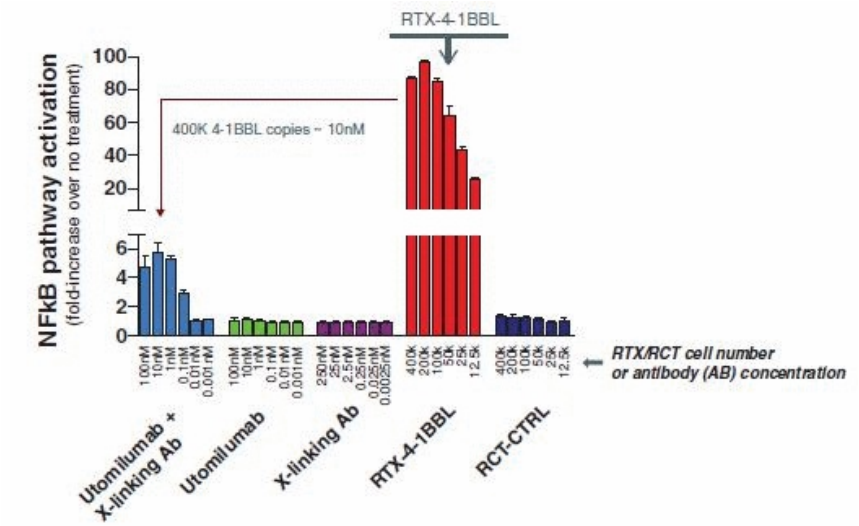
Current therapies and their limitations

Checkpoint inhibitors, such as anti-programmed death receptor-1 antibodies, or anti-PD-1 antibodies, act by inhibiting tumor suppression of the adaptive immune system in cancer patients and have significantly extended survival in multiple solid tumor types, particularly in patients with advanced cancers. The vast potential of checkpoint inhibitors is highlighted by market projections that estimate sales for this class of drugs could reach $50 billion in 2024. Despite the encouraging efficacy of checkpoint inhibition for some patients, overall response rates remain relatively low and range, on average, from 25% to 50%. Unfortunately, even when patients do respond, many still progress within six to 12 months depending on the cancer and the therapeutic intervention. Clinicians and biopharmaceutical companies are increasingly evaluating combination therapies to improve response rates and to expand the size of the treatable population.

Preclinical data for RTX-4-1BBL

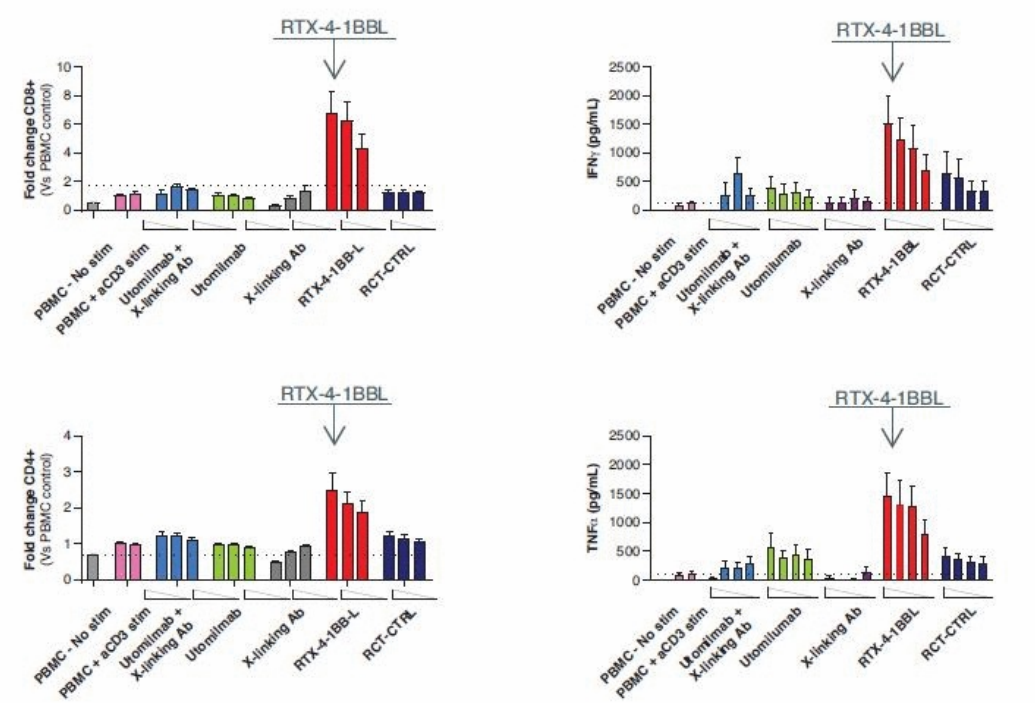
We have observed that *RTX*-4-1BBL, which expresses 4-1BBL on the cell surface, drives potent T cell activation as measured by a standard *in vitro* assay in which intracellular signaling of NFkB, a protein complex that controls immune system responses, is measured using Jurkat cells, a human T cell line. As presented in the following chart, we observed activation up to 15-fold more potent than the activation generated by the agonistic anti-4-1BB monoclonal antibody, utomilumab, which others have tested in cancer patients. We used RCT-CTRL, a cultured red cell that does not express an active protein, as a negative control. Furthermore, we observed in this *in vitro* assay that increasing the copy number of the 4-1BBL protein on RTX-4-1BBL results in a clear dose-response for immune activation. We have therefore engineered the expression of 4-1BBL on our RCT product candidates to maximize T cell activation.

NFkB Activation by RTX-**4-1BBL in Jurkat Cells**



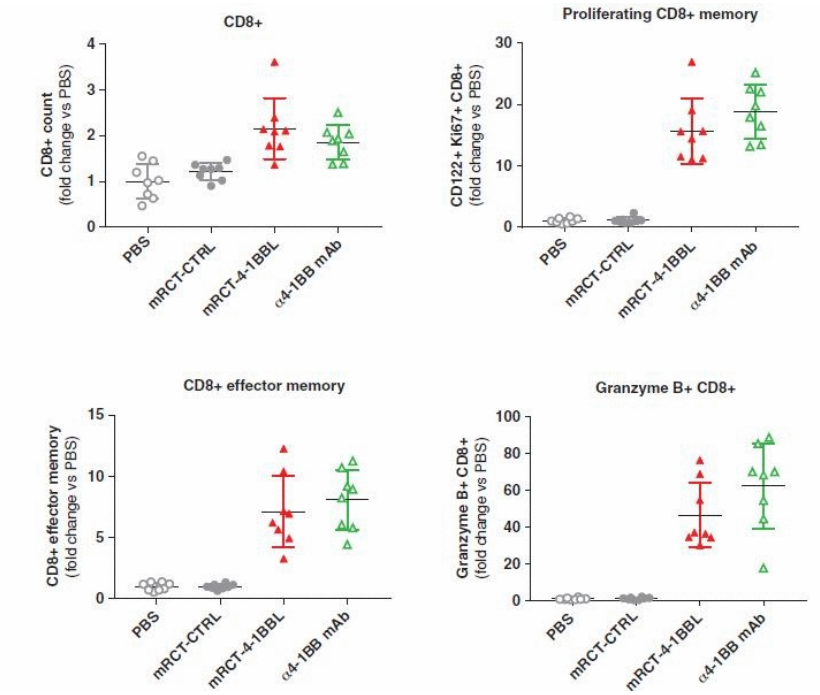
We observed that RTX-4-1BBL stimulates primary CD8+ and CD4+ T cells to proliferate and become activated, as measured by the production of two cytokines released by activated T cells that are central to the human immune response, interferon gamma (IFNγ) and tumor necrosis factor alpha (TNFα). RTX-4-1BBL stimulated a four to six-fold and two to three-fold increase in CD8+ and CD4+ T cells, respectively, and up to a three-fold increase in IFNγ and TNFα production. In contrast, utomilumab alone did not stimulate any measurable proliferation and only minimal activation of T cells when compared to RCT-CTRL. We believe that the potent T cell stimulating activity of RTX-4-1BBL is due to high expression of 4-1BBL on the cell surface in its natural, trimeric conformation, simulating the immune synapse that is formed between APCs and T cells.

In Vitro Proliferation and Activation of Primary CD8+ and CD4+ T Cells by RTX-4-1BBL



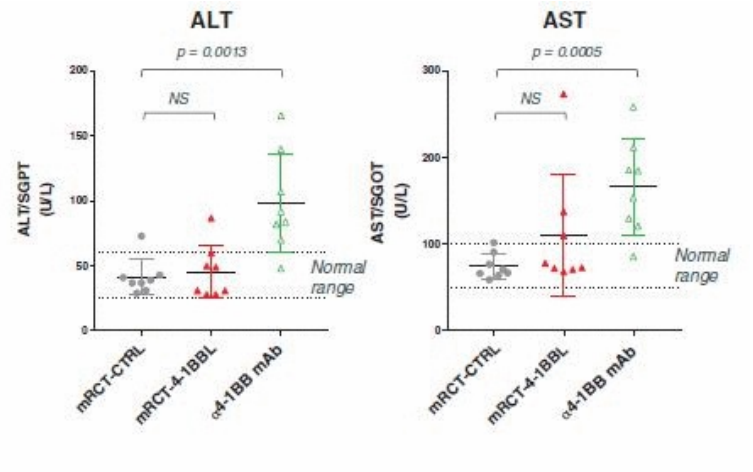
In preclinical mouse studies, we have observed that a murine version of RTX-4-1BBL, or mRCT-4-1BBL, drove potent stimulation of CD8+ T cells and key subpopulations of CD8+ T cells, such as proliferating CD8+ memory T cells, CD8+ effector T cells and Granzyme B+ CD8+ T cells, which are important for improved and sustained clinical response rates in cancer patients. The data presented in the following charts suggests that mRCT-4-1BBL is sufficient to stimulate close to maximal T cell activation and proliferation because the mRCT-4-1BBL drove similar levels of activation and proliferation of CD8+ T cells *in vivo* as a 25-fold higher dose of 3H3, an anti-mouse 4-1BB agonistic monoclonal antibody (α4-1BB mAb). The negative controls phosphate buffered saline, or PBS, and a murine control RCT that does not express an active protein, or mRCT-CTRL, did not stimulate *in vivo* proliferation of CD8+ T cells. We believe this data supports our belief that high expression of 4-1BBL on the cell surface in its natural, trimeric conformation, drives RTX-4-1BBL's potent T cell stimulating activity.

In Vivo Proliferation of CD8+ T cells and Subsets Thereof by mRCT-4-1BBL



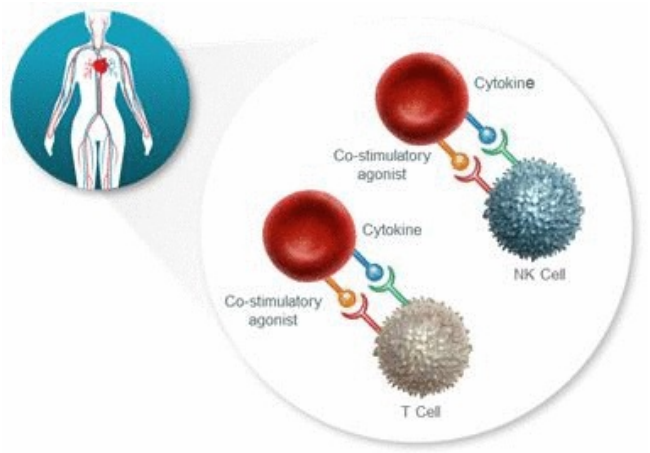
In a mouse model of liver toxicity, we observed favorable tolerability of mRCT-4-1BBL. Levels of the liver enzymes aspartate transaminase, or AST, and alanine transaminase, or ALT, were not significantly elevated following administration of mRCT-4-1BBL, as compared to administration of a mRCT-CTRL. In contrast, we observed significant elevations of the liver enzymes after administration of α4-1BB mAb. This indicates that the potent stimulation of CD8+ T cells we observed *in vivo* with mRCT-4-1BBL was not accompanied by the liver toxicities that have been associated with administration of other anti-4-1BB agonists.

Liver Toxicity in Mice of mRCT-4-1BBL Compared to α4-1BB Agonist mAb



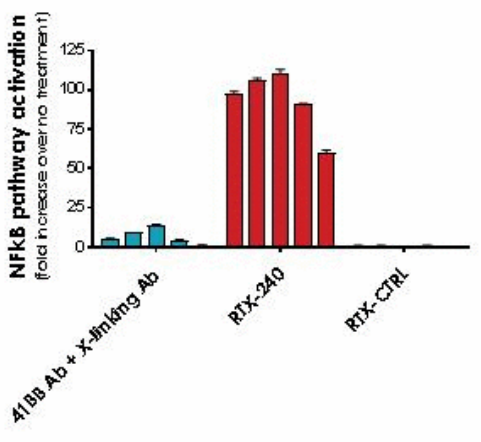
Preclinical data for RTX 240

RTX-240 co-expresses 4-1BBL and IL-15TP on the cell surface to stimulate both an adaptive and innate immune response.



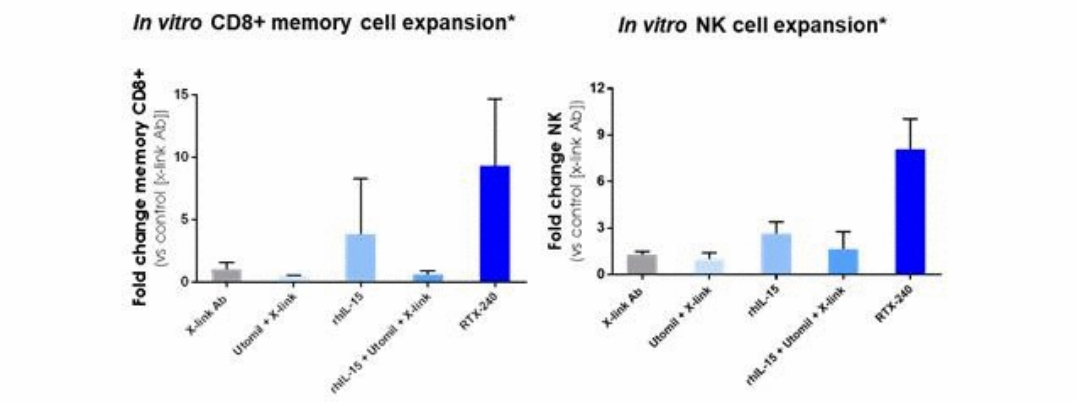
Using the Jurkat human T cell line, we observed potent T cell activation with RTX-240, as shown in the following chart. Importantly, we showed that the same level of T cell activation was not induced by molar equivalent doses of utomilumab. As expected, the control RCT, or RTX-CTRL, was also inactive.

NFkB Activation by RTX-240 in Jurkat Cells



Additionally, we have observed *in vitro* that RTX-240 can potently expand CD8+ T cells, NK cells and key subsets of these cells to a substantially greater extent than RTX-4-1BBL or RTX-IL-15TP alone, as shown in the following charts. In the absence of T cell stimulation with an anti-CD3 antibody, we observed a synergistic effect from the combination of the 4-1BBL and IL-15TP co-expressed on RTX-240 in expanding both CD8+ memory (2.5 fold) and NK cells by approximately 10-15 fold. This was substantially higher than utomilumab, rhIL-15, and a combination of utomilumab and rhIL-15.

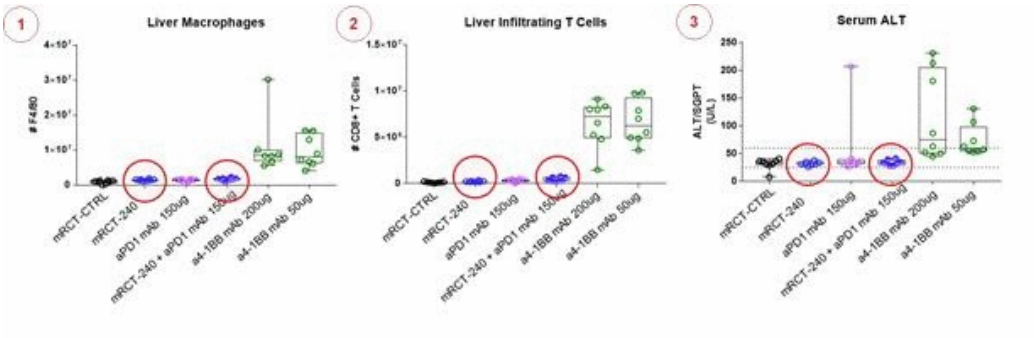
In Vitro Proliferation and Activation of CD8+ Memory Cells and NK Cells by RTX-240



In a mouse model of liver toxicity, we observed no evidence of toxicity with mRCT-240. Levels of aspartate transaminase, or AST, and alanine transaminase, or ALT, were not significantly elevated following administration of mRCT-240, as compared to administration of mRCT-CTRL. In contrast, we observed significant transaminase elevations after administration of α4-1BB mAb. Liver infiltration with macrophages and CD8+ T cells are considered to be critical to 4-1BBL-induced liver toxicity. As expected, we observed increased liver infiltration with all of these cell

populations following treatment with 4-1BB agonist antibodies. There was no increased liver infiltration with any of these cell populations following mRCT-240 treatment.

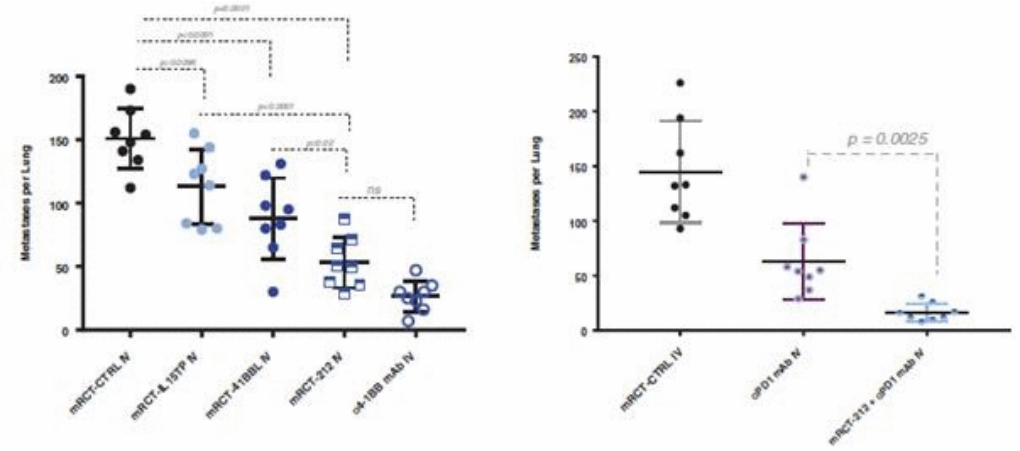
Liver Toxicity in Mice of mRCT-240 Compared to α4-1BB Agonist mAb



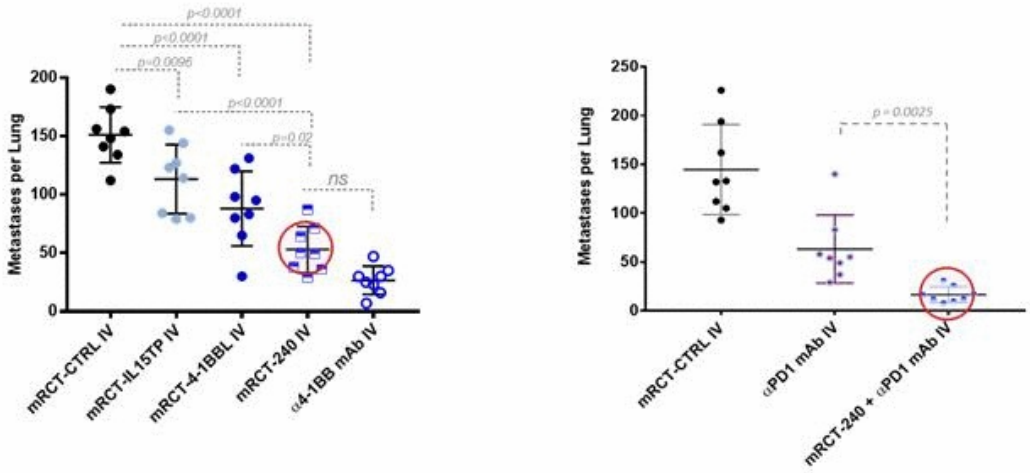
4-1BB agonistic antibodies are believed to cause liver toxicity through a multi-step process that begins with activation of bone marrow-derived monocytes, which subsequently infiltrate the liver, activating Kupffer cells and then CD8+ cells. Our data suggest that mRCT-240 does not stimulate the bone marrow derived monocytes, consistent with the hypothesis that activation occurs in the bone marrow, which has limited exposure to mRCT-240.

Our *in vivo* studies of a murine surrogate of RTX-240, mRCT-240, administered intravenously, or i.v., in a B16F10 lung metastasis mouse model provide further evidence in support of RTX-240. In this model, tumor cells were injected intravenously to establish metastases in the lung and then mice were treated with mRCT-240 alone or in combination with an anti-PD-1 antibody. mRCT-240 administered i.v. as a monotherapy reduced tumor burden in mice compared to those treated with mRCT-CTRL, mRCT-4-1BBL and mRCT-IL-15TP (left chart below), thereby indicating the potential synergy that may be achieved by expressing both 4-1-BBL and IL-15TP on the cell surface of mRCT-240. The tumor burden reduction that was observed after administration of α4-1BB mAb was not significantly different from mRCT-240. However, the observed effect of α4-1BB mAb was at the same dose level that generated hepatotoxicity in mice. As mRCT-240 did not generate liver toxicity in mice, we believe that mRCT-240, if successfully developed and approved, may have an improved therapeutic index, or improved risk-benefit, over agonistic 4-1BB antibodies in cancer patients. In a separate study mRCT-240 administered i.v. in combination with the anti-PD-1 antibody significantly reduced tumor burden in mice compared to those treated with the negative control mRCT-CTRL, as well as the anti-PD-1 antibody alone (right chart below).

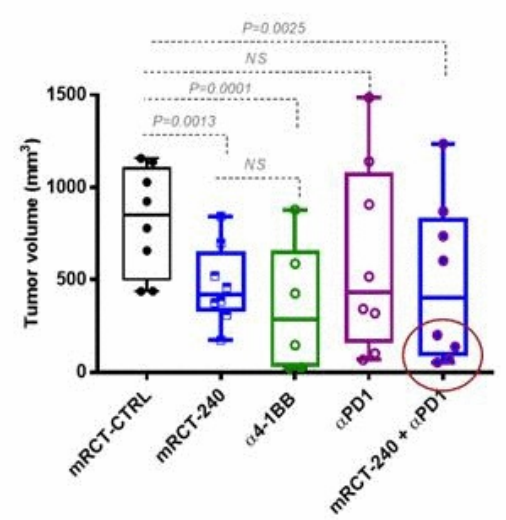
Activity of mRCT-240 in a B16F10 Lung Metastasis Mouse Model



Additionally, mRCT-240 administered i.v. as a monotherapy or in combination with an anti-PD-1 antibody reduced tumor burden in a CT26 colon cancer mouse model. Treatment with the combination of mRCT-240 plus anti-PD-1 resulted in a higher number of mice with stable disease or tumor regression compared to mRCT-240 or anti-PD-1 treatment alone. The anti-tumor activity that was observed after administration of α4-1BB mAb at the same dose level that generated hepatotoxicity in mice was not significantly different from mRCT-240. As mRCT-240 did not generate liver toxicity in mice, we believe that mRCT-240, if successfully developed and approved, may have an improved therapeutic index, or improved risk-benefit, over agonistic 4-1BB antibodies in cancer patients.



Activity of mRCT-240 in a CT26 Colon Cancer Mouse Model



In summary, we have observed that the combination of 4-1BBL and IL-15TP on RTX-240 induces potent expansion and activation of CD8+ T cells, NK cells, and key subsets of these cells. In addition, these RTX-240-mediated effects were much higher than those obtained with utomilumab, rhIL-15, and a combination of utomilumab and rhIL-15, suggesting the synergy of the combination on RTX-240 for expanding key cell types from both the adaptive and innate arms of the immune system. This potent activity translated into efficacy of mRCT-240 administered in *in vivo* cancer models of lung metastasis and colon cancer both as a monotherapy and in combination with an anti-PD-1 antibody. mRCT-240 did not generate hepatotoxicity in mice while an agonistic 4-1BB mAb did. As a result, we believe that co-expression of 4-1BBL and IL-15TP on RTX-240, and the sequestration of RTX-240 in the vasculature has the potential to drive potent anti-tumor activity with an advantageous tolerability profile. We therefore believe that the ability of RTX-240 to stimulate both the innate and adaptive immune systems will translate into therapeutic benefits for patients with solid and hematological cancers.

Clinical development

While checkpoint inhibitors have revolutionized cancer treatment, their limitations are becoming increasingly evident. Responses are confined to certain tumor types and only a limited portion of patients are cured. Currently, the challenge in immunotherapy is to extend the efficacy of checkpoint inhibitors across more tumor types as well as increase the rate and duration of response. By stimulating both arms of the immune system, RTX-240 could be an ideal combination therapy for checkpoint inhibitors to both improve and extend responses.

The MHC complex is an important nexus in the immune system because it is the way T cells recognize and kill cancer cells but it also blocks the killing function of NK cells. A common means of resistance to checkpoint inhibitors is loss of MHC expression making the cancer invisible to T cells but as a result it becomes susceptible to NK cell dependent killing. Initial clinical development of RTX-240 will include patient populations which have progressed on checkpoint inhibitor therapy due to loss of MHC expression.

We are currently completing IND-enabling studies and plan to file an IND for RTX-240 for the treatment of solid tumors by early 2020.

We are planning to evaluate RTX-240 as monotherapy and in combination with an anti-PD1 antibody, including in patients whose disease has progressed on checkpoint inhibitor therapy. We plan to identify and stratify patients whose disease has lost MHC expression. Tumor types that may be included are melanoma, non-small cell lung cancer, renal

cell carcinoma, bladder cancer, and head and neck cancer among others. Success in this population could lead to pivotal studies and development in earlier lines of therapy.

RTX-240 for hematological cancer: relapsing or refractory acute myeloid leukemia, post-HSCT

Current therapies and their limitations

Acute myeloid leukemia, or AML, is characterized by proliferation of myeloid blasts. They replace the bone marrow so that there is minimal production of platelets, red cells and neutrophils. It is primarily a disease of the elderly with a median age of diagnosis of 68. In 2017, there were more than 20,000 new cases of AML and more than 10,000 deaths caused by AML in the United States.

Standard first-line AML treatment has been unchanged for over 40 years: a regimen of intensive induction and consolidation therapy. Although most patients respond, the majority relapse over time. Therefore, many younger patients with AML undergo hematopoietic stem cell transplant, or HSCT, which can be curative if the transplant is successful. In 2016, more than 3,500 AML patients underwent allogeneic-HSCT in the United States and over 6,200 underwent the procedure in Europe.

Recently, additional therapies have been approved for treatment of AML, such as gemtuzumab ozogamicin, CPX-351, and, for patients with specific mutations, midostaurin and enasidenib. Although these therapies improve response rates and enable more patients to bridge to transplant, overall survival rates remain low.

Clinical development

The effectiveness of allogeneic HSCT depends on both the killing of residual tumor by high dose chemotherapy and on graft versus leukemia effects. NK cells are a critical component of the graft versus leukemia effect. After bone marrow ablation and allogeneic transplantation, NK cells are the first lymphocyte population to recover, but their killing and cytokine-secreting functions are limited when compared to the NK cells of healthy donors. The rate of return and function of NK cells are correlated with treatment outcome post-allogeneic HSCT, so increasing the number and function of NK cells post-allogeneic HSCT to stimulate the graft versus leukemia effect has the potential to increase survival in patients receiving allogeneic HSCT for treatment of AML. As discussed above, 4-1BBL and IL-15TP induce proliferation and maturation of NK cells, supporting the testing of RTX-240 in the post-allogeneic HSCT setting.

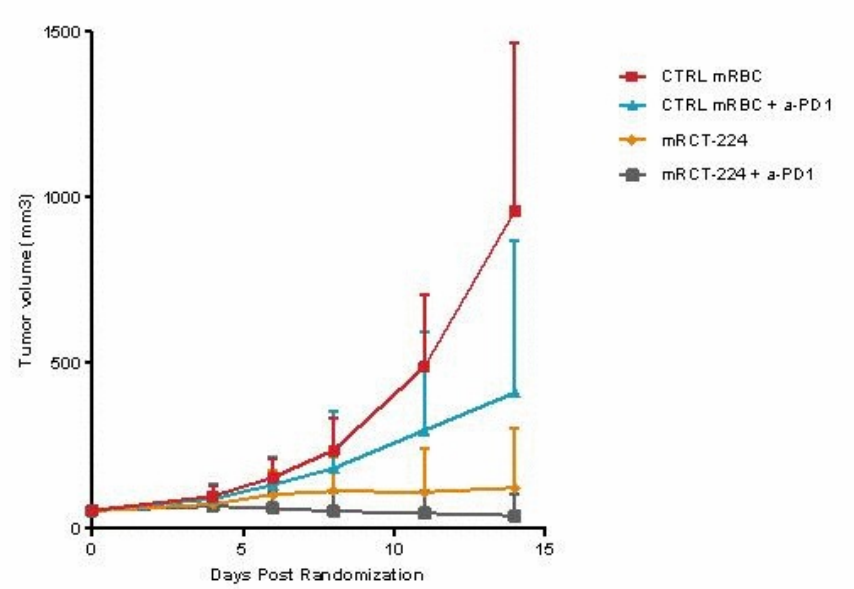
We plan to evaluate RTX-240 in AML patients post-allogeneic HSCT using the monotherapy dose determined in our initial Phase 1 trial of RTX-240 in solid tumors. Pending feedback from the FDA, we believe the primary endpoint will be relapse-free survival.

Preclinical data for RTX-224

RTX-224,our second immunotherapy product candidate, has been shown to drive both T cell and NK cell activation and expansion by simultaneously and proximately co-expressing IL-12 and 4-1BBL.

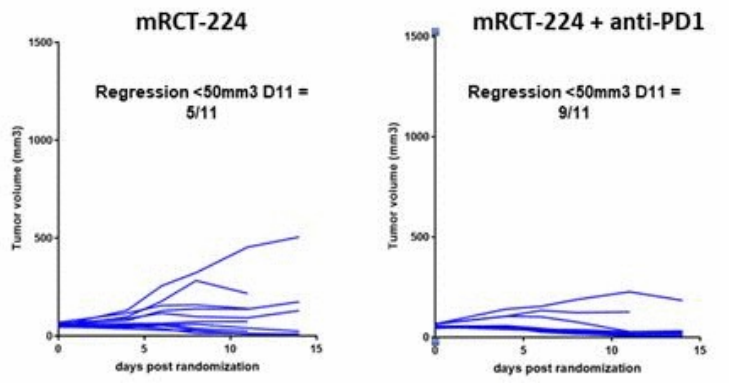
Our *in vivo* studies of a murine surrogate of RTX-224, mRCT-224, administered subcutaneously in an MC38 colon cancer mouse model provide evidence in support of RTX-224's immune activation and tumor control. In this model, tumor cells were injected to establish growing tumors and then mice were treated with a control mRBC alone, mRCT-224 alone, an anti-PD1 antibody in combination with mRBC-CTRL, or with mRCT-224 in combination with an anti-PD-1 antibody. mRCT-224 administered as a monotherapy reduced tumor burden in mice compared to those treated with mRBC-CTRL with or without and anti-PD1 antibody. Tumor control was even more pronounced when mRCT-224 was combined with an anti-PD1 antibody. These studies support the potential of RTX-224 as a potent monotherapy or combination therapy.

Activity of mRCT-224 in an MC38 Colon Cancer Mouse Model



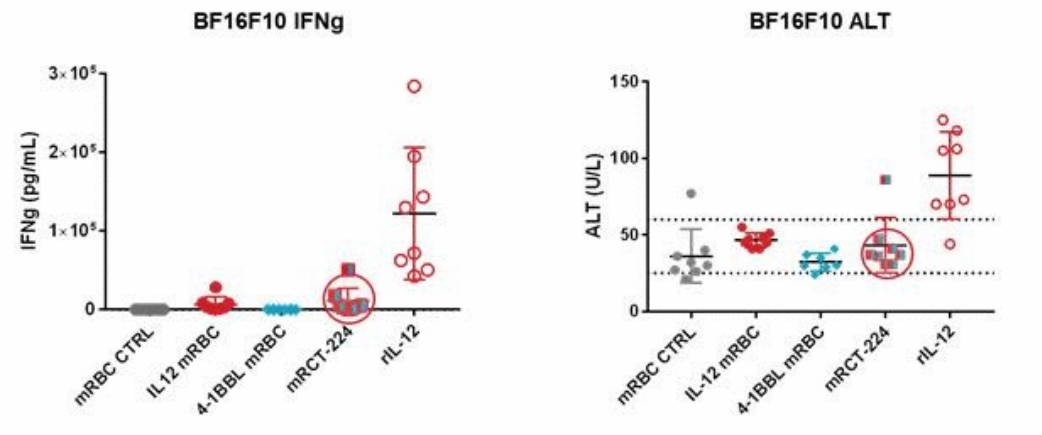
The potential of RTX-224 is further illustrated by the number of tumor regressions demonstrated in the same MC38 model. In this case, a regression is defined as a tumor volume below 50 cubic millimeters, as measured on day 11 post randomization. mRCT-224 administered alone resulted in 5/11 tumor regressions, while mRCT-224 administered in combination with an anti-PD1 antibody resulted in 9/11 tumor regressions.

Activity As Measured by Tumor Regression of mRCT-224 in an MC38 Colon Cancer Mouse Model



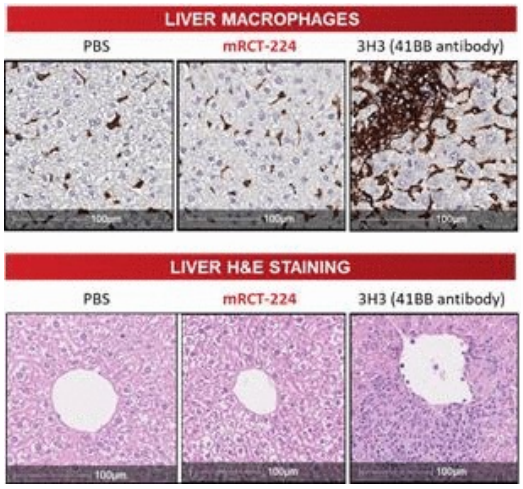
We saw no evidence of toxicity with mRCT-224. Levels of interferon gamma, or IFNg, and alanine transaminase, or ALT, were not significantly elevated following administration of mRCT-224. In contrast, we observed significant interferon gamma and transaminase elevations after administration of recombinant human interleukin 12, or rhIL-12.

Liver Toxicity in Mice of mRCT-224 Compared to rhIL-12



Histopathological examination of liver sections from RTX-224 treated mice reveal no macrophage infiltration or tissue inflammation. This is in stark contrast to control mice treated with the murine 4-1BB antibody, 3H3, where significant macrophage infiltration and tissue damage is evident. This difference between the treated and control groups was evident both with and without the co-administration of an anti-PD-1 antibody.

Liver Macrophage Infiltration and Fibrosis in Mice Associated with mRCT-224 as Compared to rhIL-12



In summary, we have observed that the combination of 4-1BBL and IL-12 on RTX-224 induces efficacy in *in vivo* cancer models both as a monotherapy and in combination with an anti-PD-1 antibody. mRCT-224 did not generate hepatotoxicity in mice while the recombinant human cytokine IL-12 did. Nor did mRCT-224 generate liver damage, while a control 4-1BB antibody did. As a result, we believe that co-expression of 4-1BBL and IL-12 on RTX-224, and the sequestration of RTX-224 in the vasculature has the potential to drive potent anti-tumor activity with an advantageous tolerability profile. We therefore believe that the ability of RTX-224 to stimulate both the innate and adaptive immune systems will translate into therapeutic benefits for patients with solid tumors.

Clinical development

While checkpoint inhibitors have revolutionized cancer treatment, their limitations are becoming increasingly evident. Responses are confined to certain tumor types and only a limited portion of patients are cured. Currently, the challenge in immunotherapy is to extend the efficacy of checkpoint inhibitors across more tumor types as well as increase the rate and duration of response. By stimulating both arms of the immune system, RTX-224 could be an ideal combination therapy for checkpoint inhibitors to both improve and extend responses.

IL-12 is known to drive the proliferation of T cells and NK cells. In turn, these activated T-cells drive antigen presentation. This antigen presentation may enable us to target formerly non-immunogenic tumors by enhancing their immune signature.

We are planning to evaluate RX-224 in solid tumors as monotherapy and in combination with an anti-PD-1 antibody. We also plan to study RTX-224 in patients whose disease has progressed on checkpoint inhibitor therapy. Success in this population could lead to pivotal studies and development in earlier lines of therapy.

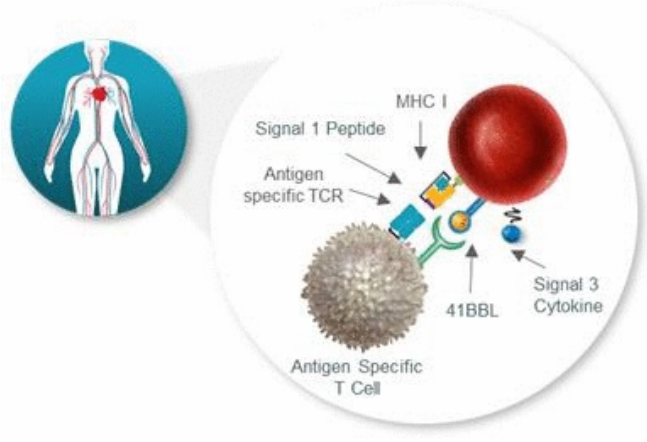
RCTs functioning as artificial antigen presenting cells (aAPCs)

We have created RCT product candidates that function as artificial APCs, or RTX-aAPCs, with the potential to induce selective anti-tumor killing by stimulating the immune system to target tumors in an antigen-specific manner.

RCTs permit us to present a variety of proteins in their native state and RTX-aAPCs take advantage of this as they co-express an MHC that presents a tumor-specific peptide, or signal 1, to the immune system together with a costimulatory protein, such as 4-1BBL, or signal 2, that stimulates the adaptive immune system. When co-expressed and delivered simultaneously and proximately, signal 1+2 promotes T cell activation/initial proliferation and potentially memory. A third cytokine signal can also be added to increase T cell expansion further and support the maintenance of T cell memory.

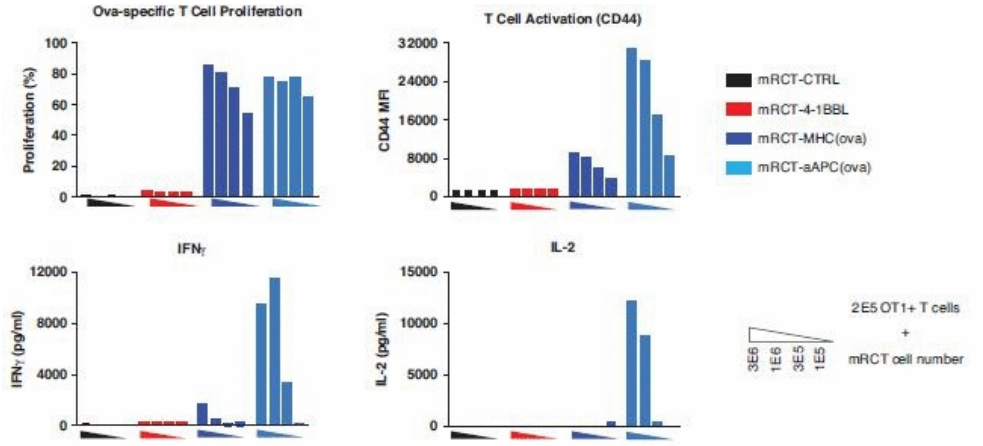
The action of the construct described mimics the normal T cell-APC interaction via the T cell receptor, or TCR, and has shown high levels of T cell expansion and activation in preclinical studies, as well as very specific tumor killing. CD8+ cytotoxic T cells respond to antigens in association with MHC I molecules, and CD4+ helper T cells respond to antigens in association with MHC II molecules. MHC I and MHC II tumor antigen presentation combined with potent co-stimulation has the potential to generate sustained tumor-specific killing. Our lead aAPC program targets HPV+ tumors, of which head and neck and cervical cancer are the most common. Treatment options for refractory and relapsing disease are limited, and we expect to be able to offer patients a potent and highly specific immune stimulation.

RTX-aAPCs Mimic the APC-T Cell Interaction to Provide Antigen Specific Cancer Therapies



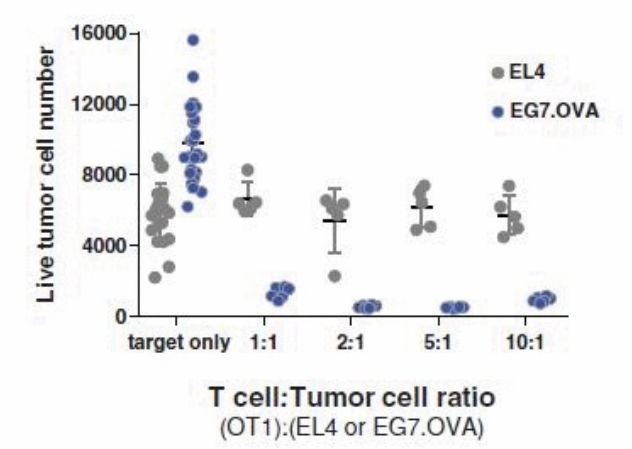
We have observed that murine RCT-MHC I (ovalbumin) co-expressed with 4-1BBL on the cell surface, or mRCT-aAPC (ova), activates ovalbumin-specific T cells *in vitro* and *in vivo,* supporting the ability to potently and selectively expand and activate an antigen-specific T cell in a dose dependent manner (increasing cell number per dose from right to left in the following charts) using our RCTs.

Activation of Ovalbumin-Specific T Cells with mRCT-aAPC (ova)



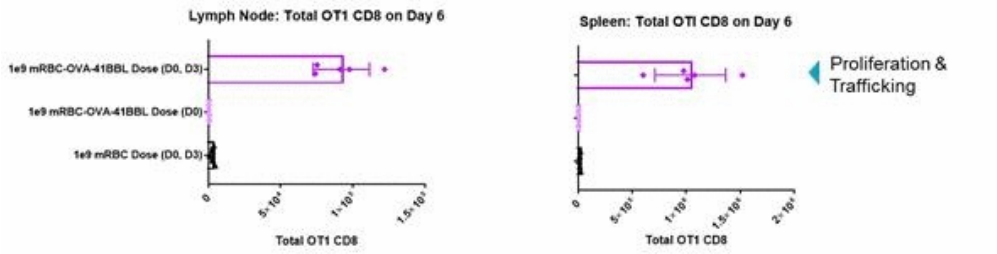
We have also observed that ovalbumin-specific T cells, or OTI-T cells, that are expanded and activated by mRCT-aAPC (ova) selectively kill ovalbumin-expressing tumor cells, or EG7.OVA cells, while the parental cells that do not express ovalbumin are not attacked and killed.

Activity of OT1-T Cells Expanded With mRCT-aAPC (ova)



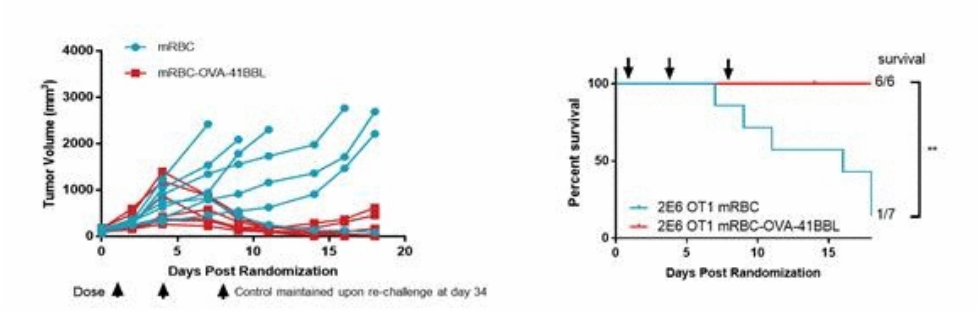
Furthermore, we have observed *in vivo* in mice that mRCT-aAPC (ova) specifically expand and activate OTI-T cells in circulation and in the spleen. Importantly, we find that the majority of the OTI-T cells display a central memory phenotype, which has been found to be a key population driving the effectiveness of T cell based therapies. In addition, a large proportion of these cells are found to traffic to lymph nodes, supporting their potential to effectively mobilize within the body and to the tumor to support a robust anti-tumor response. In contrast, mRCT-4-1-BBL without MHC I (ovalbumin) on the cell surface does not expand or activate OTI-T cells, thereby indicating that mRCT-aAPCs mimic the function of antigen presenting cells *in vivo*.

Proliferation of OT1-T Cells Expanded With mRCT-aAPC (ova) In The Lymph Node and Spleen



As noted above, OTI-T cells, that are expanded and activated by mRCT-aAPC (ova) selectively kill ovalbumin-expressing tumor cells, or EG7.OVA cells. In the experiment depicted below, following tumor cell inoculation, animals treated with three doses of mRCT-aAPC (ova) reduced tumor volume compared to those dosed with mRCT-CTRL. Control was maintained upon tumor cell re-challenge at day 35 by EG7.OVA and at day 85 by cells from the EL4 parental cell line, potentially implying the development of broad immunological memory. Further, there was a statistically significant difference in survival between the treatment and control cohorts.

Activity of OT1-T Cells Expanded With mRCT-aAPC (ova)



The ability to significantly expand and activate a tumor specific T cell population to kill tumors *in vivo* shares characteristics with CAR-T therapies which administer a tumor specific T cell population that can expand, sometimes uncontrollably, in the patient. By controlling the RTX-aAPC dose, we believe that we can more effectively control the expansion of the tumor specific T cells and potentially the tolerability and effects of the therapy.

The potential applications of RTX-aAPCs span both solid and hematological cancers and there are many known tumor antigens common to certain cancers that can be targeted for development. Over the mid-term, patient specific antigens can be sequenced to create personalized therapies. We believe that this may provide a more reliable and scalable approach to personalized cellular therapy. In addition to a program in HPV 16+ tumors, we are exploring the use of known tumor antigens, such as EBV, NY-ESO-1 and MAGE-A peptides, as well as tumor neo-antigens to deliver more accessible and effective treatments than standard vaccines or alternative neo-antigen approaches.

Cancer discovery research

Our RED PLATFORM provides significant potential to develop and advance a broad portfolio of RCTs for treatment of cancer. In addition to the lead programs described above, we are evaluating RCT product candidates that target tumors by expressing proteins that bind specifically to known tumor antigens, such as CD19, BCMA CD33, CD38 and CD123. These tumor antigen targeting RCT product candidates can be designed to kill tumors directly, to increase the persistence of existing CAR-T and TCR based therapies, or to starve and thereby kill tumors by degrading metabolites that are critical for tumor proliferation. In addition, we are evaluating a range of combinations of co-stimulatory ligands, such as OX40-L, ICOS-L and GITR-L, and cytokines, such as IL-7, IL-18 and IL-21. We believe that these approaches may provide therapeutic benefits to patients with solid or hematological cancers.

Autoimmune diseases

RCT product candidates for the induction of antigen-specific tolerance

We have generated RCT product candidates that express antigens within the cell, on the cell surface, or as presented by major histocompatibility complex II, and we believe that this represents a powerful antigen-presenting platform for the potential treatment of autoimmune diseases, such as Type 1 diabetes. We are also exploring antigen independent approaches that hold the potential to simulate specific regulatory cells which then target a range of autoreactive T cells. We believe that if successful, this approach will allow us to address a wide range of autoimmune diseases.

We are currently assessing several tolerance inducing RCT product candidates and expect to select our first clinical candidate for treatment of autoimmune diseases in 2019. We anticipate that such product candidate will focus on an indication, such as pemphigus vulgaris, where treatment effects are easily measureable and proof-of-concept can be demonstrated in an efficient manner.

Current therapies and their limitations

Over the past two decades, considerable progress has been made in the treatment of a range of autoimmune disorders with many patients enjoying an improvement in quality of life as a result. Despite their success, current therapeutic approaches to autoimmune diseases are either generally or specifically immunosuppressive and expose patients to an increased risk of opportunistic infection and hematological cancers, as is the case with JAK inhibitors, anti-TNF antibodies and anti-CD20 targeted antibodies. In up to one third of cases, patients with autoimmune diseases fail to respond to treatment, and most responding patients ultimately lose response over time.

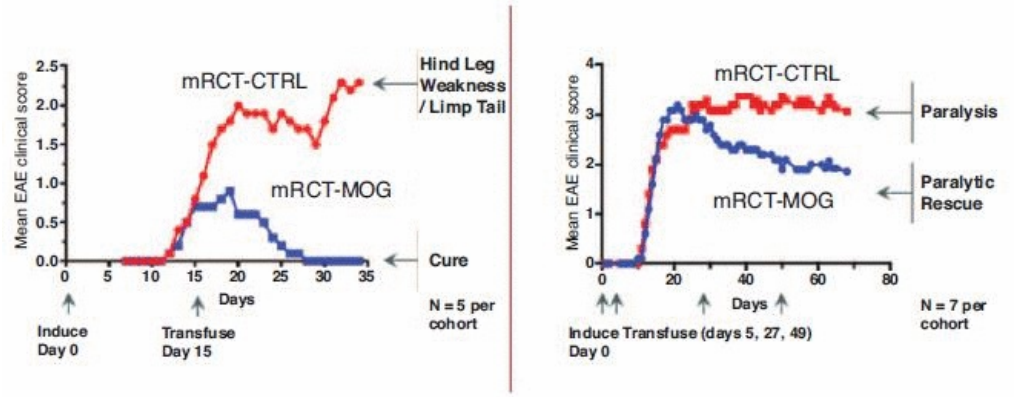
While the triggers of most autoimmune diseases remain unknown, it is generally understood that clinical disease is the result of a loss of tolerance to one's own cells. The accepted model of disease assumes a genetic susceptibility triggered by an environmental event, which leads to a breakdown of T cell-mediated immune suppression. In principle, restoration of peripheral tolerance should provide patients with a partial or complete cure.

A range of competitive approaches to peripheral tolerance restoration have been investigated over the last few decades. These include the oral administration and direct injection of a protein or peptide with or without immunosuppression, the creation of peptide bearing nanoparticles and the adoptive transfer of engineered regulatory T cells. Thus far, these approaches have not proven to be successful in late-stage clinical trials, but the field continues to progress. Direct administration of peptides and nanoparticles suffer biodistribution, stability, presentation and orientation challenges which limit the effectiveness of cell-cell signaling. To date, adoptive transfer approaches are all autologous and are hampered by some of the same handling and scalability issues that limit the application of other cellular therapies. By contrast, RCT breakdown by antigen presenting cells in the liver is thought to recapitulate the normal process of self / non-self recognition training that would lead to tolerance induction. When compared with contemporary and historical approaches of tolerance induction, RCTs could represent a clinically meaningful step forward.

Preclinical data

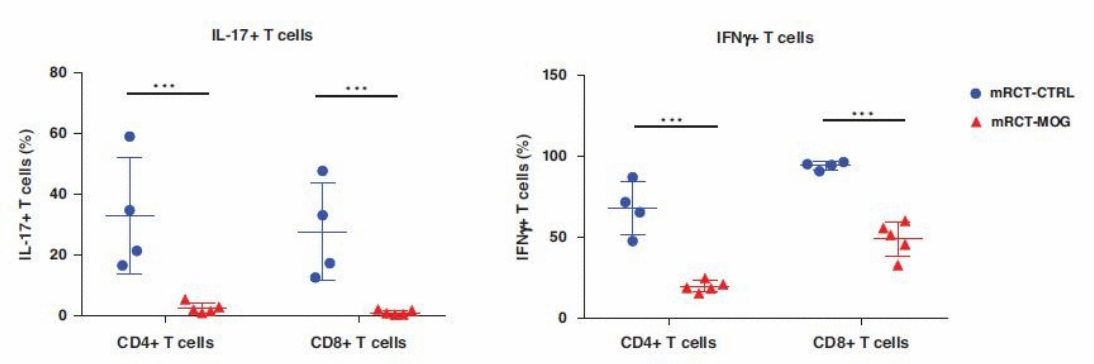
In a commonly used preclinical mouse model of neurodegeneration, the experimental autoimmune encephalomyelitis model, or EAE model, we have observed induction of peripheral tolerance using a murine RCT displaying the model-specific antigen associated with neuronal demyelination, the MOG 35-55 peptide. In the experiment depicted below, murine RCT-MOG, or mRCT-MOG, and control mouse RBCs were administered to mice at a disease score of one. The mRCT-MOG-treated animals were brought back to an average disease score of zero, while control animals continued to progress to limited disability. More significantly, as depicted in the second experiment, following treatment with mRCT-MOG and control mouse RBCs at a disease score of three, indicating that the animals were paralyzed, we observed a remarkable recovery curve following treatment with murine RCT-MOG. In effect, mice exhibiting paralysis were made to walk again.

mRCT-MOG Effect on Mice with Moderate EAE (Left) and Paralyzed EAE Mice (Right)



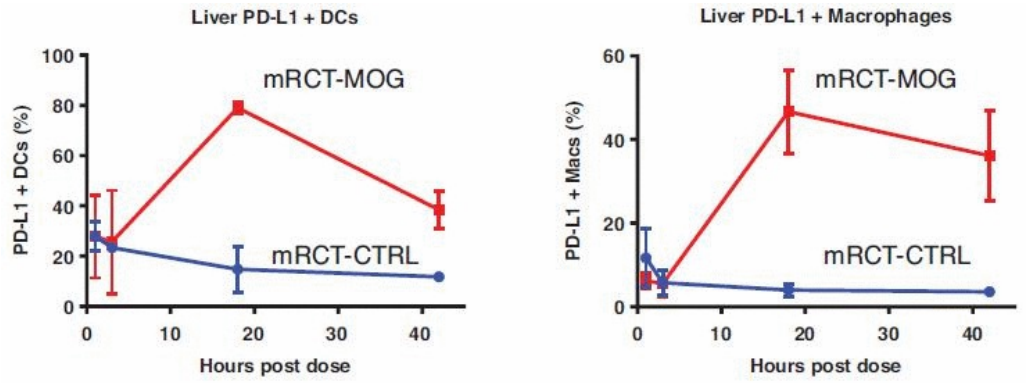
Upon examination of the histopathology, the difference in the damage to spinal cord tissue between the control and treated mice was notable. In addition, treatment with mRCT-MOG cells was found to dramatically reduce the infiltration of pathogenic Th1 and Th17 CD4+ cells that have been shown to drive disease progression.

Effect of mRCT-MOG on Th1 and Th17 Cells in the Spinal Cord in EAE Mice



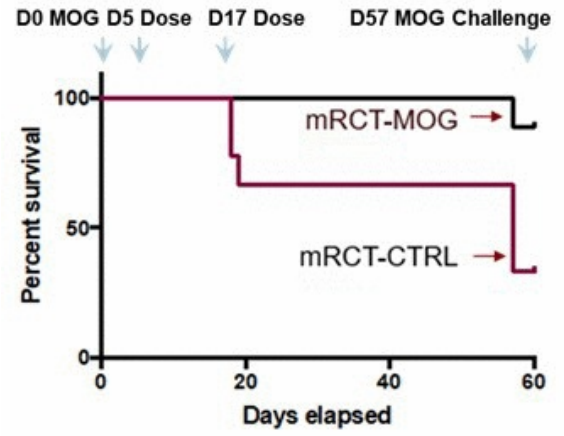
In further preclinical studies in EAE mice, we observed that mouse RBCs and mRCT-MOG cells are taken up by antigen presenting cells, such as dendritic cells (DC) and Kupffer cells within the liver, and that mRCT-MOG upregulates PD-L1, an immunosuppressive marker, on APCs, while control mouse RBCs do not. The above findings suggest that red blood cell uptake into APCs promotes an immunosuppressive phenotype that then drives the reduction in pathogenic Th1 and Th17 T cells in the spinal cord, thereby providing evidence for the mechanism of action for RCT-driven tolerance induction.

Effect of mRCT-MOG in Immunosuppressive on the Phenotype of APCs in EAE Mice



Beyond observations of therapeutic effects in this disease model, we have generated evidence of the development of immunologic memory following treatment with mRCT-MOG, suggesting the possibility of a cure. Using the EAE animal model, mice were first treated with either mRCT-MOG or control mouse RBCs on Days 5 and 17. Following a 40-day washout period after which the administered mouse RBCs were no longer in circulation, the EAE mice were re-challenged with MOG peptide to re-stimulate an immune response. We observed a clear improvement in survival between the mRCT-MOG treated group and the control group, indicating that RCT-MOG treated animals maintained immunological memory which protected them from the re-challenge.

Survival of Previously mRCT-MOG Treated EAE Mice After a Second MOG Challenge



The ability of antigen-presenting RBCs to drive tolerance induction in a preclinical model of Type 1 diabetes was recently demonstrated by our collaborators, Professors Hidde Ploegh and Harvey Lodish. In their study, NOD/ShiltJ mice, a strain genetically engineered to develop Type 1 diabetes after 10 to 13 weeks, were either treated with control RBCs or with RBCs that displayed a peptide consisting of the amino acids 9-23 of insulin B-chain on the cell surface. All mice receiving control RBCs became hyperglycemic while most mice receiving RBCs displaying the insulin peptide were protected from Type 1 diabetes onset and remained normoglycemic.

Overall, we and our collaborators have generated compelling preclinical evidence in support of applying antigen-expressing RCT product candidates to induce antigen-specific tolerance for the treatment of a range of autoimmune diseases.

Autoimmune disease discovery research

Beyond developing RCTs that express one or more antigens for the treatment in antigen-induced autoimmune diseases, we are exploring the potential to apply RCT product candidates to stimulate specific populations of regulatory T cells directly and direct the immune system back to a more tolerogenic state. We have also created RCT constructs that clear lethal doses of TNF-alpha and botulinum toxin from the bloodstream of mice, suggesting that RCTs may also provide therapeutic benefits to patients suffering from severe inflammatory diseases.

Manufacturing

We have industrialized the production of RCTs by developing and scaling up a manufacturing process by which hematopoietic progenitor cells are expanded, then genetically engineered and subsequently differentiated and matured into fully enucleated RCTs that express biotherapeutic proteins within the cell or on the cell surface. Our standard RCT manufacturing process includes the following steps:

(1) Donors are screened for infectious diseases according to regulatory guidelines and are typed for major blood group antigens. O negative blood donors are selected and administered granulocyte colony stimulating factor to mobilize their bone marrow.

(2) CD34+ hematopoietic precursor cells are isolated from universal donor blood, collected by apheresis and purified.

(3) These precursor cells are expanded and then transduced using a lentiviral vector encoding one or more chosen biotherapeutic proteins.

(4) The cells are then exposed to a defined media formulation to promote further expansion and differentiation until they differentiate and mature into enucleated reticulocytes. At this stage, the enucleated reticulocytes are RCTs that express one or more biotherapeutic proteins in the cytosol or on the cell surface.

(5) The RCTs are purified to separate the mature RCTs from nucleated erythroid precursor cells, formulated and stored at 4°C or frozen.

A single donor will allow us to manufacture up to thousands of doses. With approximately 7% of the U.S. population having an O negative blood type, we believe that there is ample supply of CD34+ hematopoietic precursor cells needed to produce our RCTs. Additionally, due to the inherent properties of RBCs, RCTS can be manufactured in large bioreactors using our proprietary cell culture processes, which could result in the cost of goods sold being significantly lower than other cellular therapies.

The FDA has reviewed our RCT manufacturing process, including in-process control parameters. Based on guidance from the FDA, we have established a path to production of current good manufacturing practices, or cGMP, grade product candidates for clinical use. We expect to be able to use the same or similar manufacturing processes for all our future RCT product candidates, which would enable us to bring RCTs into clinical development in an accelerated manner.

Based on our expertise in red cell biology and advice from leading hematologists and blood transfusion experts, we have developed RCT product release criteria to determine the purity, viability, red cell identity and potency of each RCT batch. These release criteria have been reviewed and accepted for clinical use by the FDA.

We are manufacturing RCTs in single use bioreactors, which enable us to control critical process parameters and thereby produce consistent RCTs that meet the established product release criteria. We currently use external suppliers for lentiviral vector production but have established an internal lentiviral vector production process. We are currently working to further increase yields and to scale into larger bioreactors.

In addition to the standard RCT manufacturing process, we have developed alternative proprietary processes for engineering hematopoietic precursor cells and maturing these into RCTs. These processes may be utilized in the production of future RCTs.

Suppliers and contract manufacturing organizations

We have entered into a clinical supply agreement with a contract manufacturing organization, or CMO, located in the United States to produce cGMP grade RTX-134 for our initial clinical trials and have successfully transferred our manufacturing process to this CMO. We have secured options for additional manufacturing suites for cGMP production of the RCT product candidates that are projected to begin clinical trials in 2020. We anticipate that these arrangements will be sufficient for the manufacture of our product candidates until our planned manufacturing facility is established and operational.

We have also entered into agreements with a supplier of cGMP grade plasmids for lentiviral production as well as a supplier of lentiviral vector. We have secured cGMP lentiviral vector production slots that we believe will be sufficient to supply RTX-134 drug product for our planned Phase 1b trial in PKU patients, and we are continually securing additional lentiviral production slots for the additional RCT product candidates that are projected to enter clinical trials.

Expanding our manufacturing capacity and supply chain

In 2018, we acquired a 135,000 square foot GMP manufacturing facility in Smithfield, Rhode Island. We are in the process of renovating and customizing this facility to contain multiple RCT GMP manufacturing suites and lentiviral vector GMP manufacturing suites. This will enable us to manufacture multiple RCTs as well as lentiviral vectors in a cGMP compliant manner for the clinical supply and, if approved, expand capacity for commercial supply of our RCT

product candidates. We plan to utilize this facility to provide clinical supply for the pivotal trial of RTX-134 and in parallel provide clinical supply for additional clinical trials with other RCT product candidates.

Intellectual property

We believe the breadth and depth of our intellectual property is a strategic asset that has the potential to provide us with a significant competitive advantage. We strive to protect and enhance the proprietary technology, inventions and improvements that are commercially important to our business, including seeking, maintaining and defending patent rights, whether developed internally or licensed from our collaborators or other third parties. Our policy is to seek to protect our proprietary position by, among other methods, filing patent applications in the United States and in jurisdictions outside of the United States related to our proprietary technology, inventions, improvements and product candidates that are important to the development and implementation of our business. We also rely on trade secrets and know-how relating to our proprietary technology and product candidates, continuing innovation and in-licensing opportunities to develop, strengthen and maintain our proprietary position in the field of engineered red cell therapeutics. We additionally rely on data exclusivity, market exclusivity and patent term extensions when available and plan to seek and rely on regulatory protection afforded through orphan drug designations. Our commercial success may depend in part on our ability to obtain and maintain patent and other proprietary protection for our technology, inventions and improvements; to preserve the confidentiality of our trade secrets; to maintain our licenses to use intellectual property owned by third parties; to defend and enforce our proprietary rights, including our patents; and to operate without infringing on the valid and enforceable patents and other proprietary rights of third parties.

We believe that we have a strong global intellectual property position and possess substantial know-how and trade secrets relating to our proprietary product candidates, technology and platform, including related manufacturing processes and technology. As for our product candidates, platform, and the processes we develop and commercialize, in the normal course of business, we pursue, as appropriate, patent protection or trade secret protection relating to compositions, methods of use, treatment of indications, dosing, formulations and methods of manufacturing. As of February 28, 2019, our patent portfolio consists of 26 patent families, including one owned U.S. issued patent, two allowed U.S. patent applications, 42 owned or in-licensed U.S. pending patent applications (including provisional applications), and 70 owned or in-licensed pending patent applications in jurisdictions outside of the United States (including Patent Cooperation Treaty, or PCT, applications) that, in many cases, are counterparts to the foregoing U.S. patents and patent applications. Our objective is to continue to expand our portfolio of patents and patent applications in order to protect our product candidates and certain aspects of our RED PLATFORM and our manufacturing processes. Examples of the products and technology areas covered by our intellectual property portfolio are described below.

Disease-related intellectual property

The disease-related patent rights in our intellectual property portfolio relate to pathological conditions and disorders and provide coverage for RCT product candidates to specifically address those conditions and the associated disease states. The disease-related patent applications for our lead programs include those described below. Each of the disease-related patent rights and applications described below are owned by us and are not licensed from any third party:

RTX-134 for phenylketonuria

Our RTX-134 program targets phenylketonuria, for which we have developed an RCT product candidate that expresses phenylalanine ammonia lyase, or PAL, an enzyme that metabolizes phenylalanine.

- This aspect of our patent portfolio relates to RCTs that express PAL, methods of treating diseases (*e.g.*, phenylketonuria) that involve accumulation of phenylalanine and methods of making of RCTs that express PAL.

- As of February 28, 2019, the patent rights relating to this technology include one issued U.S. patent related to methods of treating phenylketonuria with RTX-134, one allowed U.S. patent application related to methods of decreasing blood phenylalanine levels with RTX-134, two pending U.S. patent applications and seven pending international patent applications that have entered the National Stage (or the Seven National Stage Applications) related to RCT compositions of matter, methods of treating elevated phenylalanine levels and method of making

RTX-134. We expect the issued patent and patent applications in this portfolio, if issued, to expire in 2034, excluding any patent term adjustments or extensions.

RTX-Uricase for chronic refractory gout

Our RTX-Uricase program targets chronic refractory gout, for which we have developed an RCT product candidate that expresses uricase, an enzyme that metabolizes uric acid, and a uric acid transporter.

- This aspect of our patent portfolio relates to RCTs that express uricase and other enzymes that degrade uric acid, methods of treating diseases, for example, chronic refractory gout, that involve accumulation of uric acid, and methods of making RCTs, including RTX-Uricase, that degrade uric acid.

- As of February 28, 2019, the patent rights relating to this technology includes five pending U.S. patent applications (including provisional patent applications), and seven pending international patent applications that have entered the National Stage (i.e., the Seven National Stage Applications) related to RCT compositions of matter, methods of treating chronic refractory gout and methods of making engineered erythroid cells that express enzymes that degrade uric acid. We expect the patent applications in this portfolio, if issued, to expire between 2034 and 2039, without taking into account any patent term adjustments or extensions we may obtain.

RTX-Cystathionine beta synthase (CBS) for homocystinuria

Our RTX-CBS program targets homocystinuria, for which we have developed an RCT product candidate that expresses cystathionine beta synthase, an enzyme that metabolizes homocysteine.

- This aspect of our patent portfolio relates to RCTs that express CBS and other enzymes that reduce homocysteine levels, methods of treating homocystinuria, methods of reducing homocysteine levels and methods of making RCTs, including RTX-CBS, that reduce homocysteine levels.

- As of February 28, 2019, the patent rights relating to this technology includes four pending U.S. patent applications (including provisional patent applications) and seven pending international patent applications that have entered the National Stage (i.e., the Seven National Stage Applications) related to RCT compositions of matter, methods of treating homocystinuria and methods of making engineered erythroid cells comprising enzymes that reduce homocysteine. We expect the patent applications in this portfolio, if issued, to expire between 2034 and 2039, without taking into account any patent term adjustments or extensions we may obtain.

Additional rare disease intellectual property

In addition to our rare disease programs in PKU, chronic refractory gout and homocystinuria, our patent applications also relate to novel RCT compositions and their use for treating additional disorders that would benefit from enzyme replacement therapy, including disorders in carbohydrate metabolism, amino acid metabolism, organic acid metabolism, mitochondrial metabolism, fatty acid metabolism, purine-pyrimidine metabolism, steroid metabolism, peroxisomal function and lysosomal storage.

We expect the patent applications in this portfolio, if issued, to expire in 2034 and 2039, without taking into account any patent term adjustments or extensions we may obtain.

RTX-240 and RTX-224 for certain oncology indications

We have developed RTX-240, an RCT product candidate that co-express 4-1BBL and IL-15TP (a fusion of the cytokine IL-15 and IL-15 receptor alpha), for the treatment of patients suffering from hematological or solid cancers that have lost response to conventional therapies, including anti-PD-1 therapies or other immune-oncology therapies, and prevent the emergence of resistance to checkpoint inhibitors and other immune-oncology therapies. We have developed RTX-224, an RCT product candidate that co-express 4-1BBL and IL-12, for the treatment of patients suffering from hematological or solid cancers that have lost response to conventional therapies, have failed to qualify for or respond to or have lost

response to immunotherapy, including anti-PD-1 therapies or other immune-oncology therapies, and to prevent the emergence of resistance to checkpoint inhibitors and other immune-oncology therapies.

- This aspect of our patent portfolio relates to RCTs that express 4-1BBL, RCTs that express IL-15 or IL-15TP, RCTs that express IL-12, RCTs that co-express 4-1BBL and IL-15TP, RCTs that co-express 4-1BBL and IL-12, methods of activating CD8+ T cells and NK cells, methods of treating cancer, methods of making RCTs that express 4-1BBL and IL-15TP, including RTX-240, and methods of making RCTs that express 4-1BBL and IL-12, including RTX-224.

- As of February 28, 2019, the patent rights relating to this technology includes nine pending U.S. patent applications (including provisional patent applications) and 12 pending international patent applications that have entered the National Stage related to RCT compositions of matter, methods of activating immune cells, methods of treatment and methods of making RTX-240 and RTX-224. We expect the patent applications in this portfolio, if issued, to expire between 2037 and 2039, without taking into account any patent term adjustments or extensions we may obtain.

Additional oncology intellectual property

We own disease-related patent applications directed to RCTs for use in oncology, including immuno-oncology. These patent applications relate to RCT compositions that comprise a variety of agents, including anti-tumor antibodies, tumor starvation enzymes, pro-apoptotic proteins, costimulatory molecules, immune checkpoint inhibitors, tumor antigens, MHC molecules and numerous combinations thereof. These patent applications also cover the use of RCTs to treat cancer, including lung cancer, melanoma, renal cancer, bladder cancer, gastric cancer, squamous cell carcinoma, Hodgkin lymphoma, hepatocellular carcinoma, Merkel cell carcinoma, colorectal cancer and acute myeloid leukemia, as well as various relapsed or refractory cancers.

These disease-related patent applications include patent applications directed to RCTs that function as artificial antigen-presenting cells. These applications cover RCTs expressing combinations of MHC, antigen and a costimulatory molecule, methods of activating an antigen-specific T cell and methods of treating cancer by inducing a tumor-specific immune response.

We expect the patent applications in this portfolio, if issued, to expire between 2034 and 2038, without taking into account any patent term adjustments or extensions we may obtain.

Autoimmune disease intellectual property

We own disease-related patent applications directed to RCTs for use in treating autoimmune diseases. These patent applications relate to RCT compositions having autoimmune antigens, anti-cytokine antibodies, agents for cleaving autoimmune antibodies and numerous combinations thereof. The RCTs covered by these patent applications operate through various mechanisms, including through induction of tolerance to self-antigens, clearance of autoimmune antibodies from the bloodstream, clearance of cytokines from the bloodstream and inactivation of autoimmune antibodies. The patent applications also cover the use of these RCTs to treat a number of diseases, such as pemphigus vulgaris, Type 1 diabetes, membranous nephropathy, autoimmune hepatitis, myasthenia gravis, celiac disease and neuromyelitis optica.

We expect the patent applications in this portfolio, if issued, to expire between 2035 and 2038, without taking into account any patent term adjustments or extensions we may obtain.

Cardio-metabolic disorders intellectual property

We own a disease-related PCT application directed to RCT compositions and their use in treating cardiac disorders and metabolic disorders, including diabetes, obesity heart failure, atherosclerosis and hemophilia. We expect that any national phase patent applications filed in connection with this PCT application, if issued, to expire in 2037, without taking into account any patent term adjustments or extensions we may obtain.

Infectious disease intellectual property

We own disease-related patent applications directed to RCT compositions and their use in treating infectious diseases, such as a viral infection (*e.g.*, cytomegalovirus or HIV) or a bacterial infection (*e.g.*, bacteremia). We expect the patent applications in this portfolio, if issued, to expire between 2037 and 2039 without taking into account any patent term adjustments or extensions we may obtain.

Platform-related intellectual property

In addition to the disease-related intellectual property, our intellectual property portfolio also includes know-how and patent applications directed to the RED PLATFORM and other technologies developed internally and exclusively in-licensed from the Whitehead Institute for Biomedical Research, or WIBR, that relate to the engineering and culturing of RCTs. Exemplary platform technologies that are the subject of such patent applications include:

- methods related to the *in vitro* production of enucleated red blood cells;
- gene editing and transcriptional modulation systems for engineering RCTs;
- targeted lipid nanoparticle compositions and RNA delivery techniques;
- amplifiable nucleic acid constructs for optimizing protein production;
- methods for chemically conjugating biotherapeutic proteins to cell surfaces; and
- methods for increasing percent enucleation during RCT production.

These platform technologies, and our intellectual property protection related thereto, are broadly applicable to our RCT product candidates.

We continually assess and refine our intellectual property strategy as we develop new platform technologies and product candidates. To that end, we are prepared to file additional patent applications if our intellectual property strategy requires such filings, or where we seek to adapt to competition or seize business opportunities. Further, we are prepared to file patent applications, as we consider appropriate under the circumstances, relating to the new technologies that we develop. In addition to filing and prosecuting patent applications in the United States, we often file counterpart patent applications in additional countries where we believe such foreign filing is likely to be beneficial, including but not limited to Australia, Brazil, Canada, China, Europe, Hong Kong, India, Israel and Japan.

Individual patents extend for varying periods of time, depending upon the date of filing of the patent application, the date of patent issuance and the legal term of patents in the countries in which they are obtained. Generally, patents issued for applications filed in the United States are effective for 20 years from the earliest effective filing date. In addition, in certain instances, a patent term can be extended to recapture a portion of the term effectively lost as a result of the FDA regulatory review period. The restoration period cannot be longer than five years and the total patent term, including the restoration period, must not exceed 14 years following FDA approval. The duration of patents outside of the United States varies in accordance with provisions of applicable local law, but typically is also 20 years from the earliest effective filing date. However, the actual protection afforded by a patent varies on a product-by-product basis, from country-to-country, and depends upon many factors, including the type of patent, the scope of its coverage, the availability of regulatory-related extensions, the availability of legal remedies in a particular country and the validity and enforceability of the patent.

Trademark protection

As of February 28, 2019, our trademark portfolio contains approximately 38 registrations and pending applications. For the RUBIUS THERAPEUTICS mark, we have pending applications in the United States, Canada and Brazil, as well as an International Registration designating China, the E.U., India, Japan and Russia. Under this International Registration, the mark is pending in the E.U. and India, and registered in China, Japan and Russia. In addition, we have a U.S. trademark registration and a pending U.S. application for the RUBIUS mark. For the RCT mark, we have a pending U.S. application as well as an International Registration designating China, the E.U., India, and Japan. Under this

International Registration, the mark is pending in China and Japan, and registered in the E.U. and India. In addition, we have a pending application for this mark in Canada. We also have pending U.S. and Canadian applications for the RED CELL THERAPEUTICS mark as well as an International Registration designating China, the E.U., India, and Japan. Under this International Registration, the mark is registered in Japan and pending in the other countries. We have a U.S. trademark registration for the RED PLATFORM mark, as well as an International Registration designating China, the E.U., India, Japan and Russia. Under this International Registration, the mark is registered in China, the E.U. and Russia, and pending in India and Japan. In addition, we have a pending application for this mark in Canada. Finally, we have pending U.S. applications for the RTX mark and the REALIZING THE POWER OF RED mark.

Trade secrets

We may also rely, in some circumstances, on trade secrets to protect our technology and aspects of our platform. However, trade secrets are difficult to protect. We seek to protect our technology and product candidates, in part, by entering into confidentiality agreements with those who have access to our confidential information, including our employees, contractors, consultants, collaborators and advisors. We also seek to preserve the integrity and confidentiality of our proprietary technology and processes by maintaining physical security of our premises and physical and electronic security of our information technology systems. Although we have confidence in these individuals, organizations and systems, agreements or security measures may be breached and we may not have adequate remedies for any breach. In addition, our trade secrets may otherwise become known or may be independently discovered by competitors. To the extent that our employees, contractors, consultants, collaborators and advisors use intellectual property owned by others in their work for us, disputes may arise as to the rights in related or resulting know-how and inventions. For this and more comprehensive risks related to our proprietary technology, inventions, improvements and products, please see the section on "Risk factors—Risks related to intellectual property."

Licenses

In January 2016, we entered into an exclusive license with WIBR that grants us an exclusive, worldwide, sublicensable license under patent rights comprising two patent families to research, develop, make and commercialize products and processes covered by such patent rights for all uses, or the WIBR License. The WIBR License also includes an option to for us to exclusively negotiate with WIBR for a license to certain improvement technologies related to the licensed subject matter. The WIBR License was amended in December 2017 to grant us an exclusive license to the commercialization rights under a third patent family jointly owned by WIBR and Tufts University, or Tufts. The WIBR License was amended in July 2018 to grant us an exclusive license to the commercialization rights under a fourth patent family owned by WIBR. As of February 28, 2019, the patent portfolio licensed from WIBR consists of one allowed U.S. patent application, and a total of 13 pending U.S. and foreign patent applications. We expect these WIBR-licensed patent applications, if issued, to expire between 2034 and 2038, without taking into account any patent term adjustments or extensions that may be obtained.

The patent rights licensed to us under the WIBR License are directed, in part, to the *in vitro* production of RBCs and the use of the enzyme sortase to conjugate a protein of interest to the cell surface. We have certain diligence obligations under the WIBR License, which include using commercially reasonable efforts to develop and commercialize any products under the patents and achieving certain milestones as further described in the WIBR License. Additionally, under certain circumstances, we may in the future be obligated to negotiate in good faith field-limited, non-exclusive sublicenses to allow third parties to exploit the patent rights licensed to us under the WIBR License to develop and commercialize products that are not competitive with our products or product candidates.

WIBR retains the right with respect to all four patent families licensed to us to (i) to practice the patent rights licensed under the agreement for research, teaching and educational purposes, including sponsored research and collaboration, and (ii) to grant non-exclusive licenses to academic and not-for-profit research institutes to practice under the patent rights for research, teaching and educational purposes (excluding sponsored research), while Tufts retains such rights only with respect to the patent family that it co-owns. Pursuant to a Defense Advanced Research Projects Agency agreement between WIBR and a global biopharmaceutical company, the biopharmaceutical company funded research resulting in one of the licensed patent families and WIBR granted the right to retain a worldwide, irrevocable, non-exclusive, royalty-free right to use this patent family for research and development purposes. In addition, under the

WIBR agreement, the U.S. federal government retains a royalty-free, non-exclusive, non-transferable license to practice any government-funded invention claimed in the patent rights, as set forth in 35 U.S.C. §§ 201-211 and Executive Order 12591.

As partial consideration for the license, we issued 366,667 shares of our common stock to WIBR. In addition, we paid WIBR an upfront payment and are required to pay annual license maintenance fees, creditable against royalties and milestone payments. We are obligated to pay to WIBR low single-digit royalties based on annual net sales by us, our affiliates and our sublicensees of licensed products and licensed services that are covered by a valid claim of the licensed patent rights at the time and in the country of sale. On a country-by-country basis, upon expiration of the last valid claim of the licensed patent rights covering such licensed product or licensed service in such country, our license becomes royalty-free, perpetual and irrevocable with respect to such country. Based on the progress we make in the advancement of products covered by the licensed patent rights, we are required to make aggregate milestone payments of up to $1.6 million upon the achievement of specified preclinical, clinical and regulatory milestones. In addition, we are required to pay to WIBR a percentage of the non-royalty payments that we receive from sublicensees of the patent rights licensed to us by WIBR. This percentage varies from low single digits to low double digits and will be based upon the clinical stage of the product at the time of the sublicense.

Under the WIBR License, WIBR controls the prosecution and maintenance of the patent rights licensed to us and we have the right to review and comment on such prosecution and maintenance. We have the first right to enforce the patent rights licensed to us against third party infringers. We may terminate the WIBR License for convenience upon three months prior written notice to WIBR. WIBR may terminate the WIBR License upon written notice to us if we, along with our affiliates and sublicensees, cease to carry on business related to the WIBR License for more than six months. WIBR may terminate the WIBR License for our material breach that remains uncured for sixty days after receiving notice thereof, if we fail to pay amounts due under the agreement within thirty days after receiving notice of such failure, or if we challenge the validity or enforceability of any of the licensed patent rights.

Competition

In addition to the product specific competitors that are described for each of the initial targets we are pursuing, we have identified four companies that are leveraging the RBC as a platform. Erytech Pharma SA is using hypotonic enzyme loading to create products for use in cancer, rare diseases and immunology. The company has completed a successful Phase 3 program in acute lymphoblastic leukemia, recently failed a Phase 2 trial in acute myeloid leukemia, and completed a successful Phase 2 program in pancreatic cancer. We believe that there are three fundamental challenges with hypotonic loading:

- The hypotonic loading process may be challenging to scale as it requires delivery of hypotonically loaded blood to the patient within 72 hours of acquisition of the blood. Thus, while not autologous, it suffers from many of the shortcomings of autologous therapy.

- Therapeutic interventions are limited to agents that can be loaded into, as opposed to expressed on, the cell surface of RBCs.

- Hypotonic loading may damage the cell and impact circulating half-life.

There are three other companies that rely on loading of mature RBCs: Orphan Technologies Ltd., which is developing a range of products aimed at rare diseases; EryDel SpA, which is in late-stage development of dexamethasone loaded RBCs for the treatment of ataxia telangiectasia; and SQZ Biotechnologies, which is pursuing preclinical applications in cancer, enzyme replacement therapy and immune tolerance. Taking an alternative approach, Kanyos Bio, Inc. and Anokion SA are developing proteins that, when injected, fuse *in vivo* to the RBC binding peptide glycophorin A. The applications are preclinical, with a focus on peripheral tolerance induction.

Outside of RBC-based competition, there are companies developing engineered enzymes and specializing in rare diseases, such as Codexis, Inc., which has a product candidate in Phase 1 development for the treatment of PKU and Aeglea BioTherapeutics, Inc., which has a product candidate in a Phase 1 trial for the treatment of hyperargininemia.

There are a number of gene therapy companies, such as BioMarin Pharmaceutical, Inc., which has active gene therapy programs that include a preclinical PKU product candidate, and Homology Medicines, Inc., which recently declared that it is in IND-enabling studies with a gene therapy product candidate and expects to initiate a clinical trial in PKU in the first quarter of 2019. Moderna, Inc. is in early preclinical work with an mRNA approach to addressing PKU. In addition, Synlogic, Inc. is one of several companies developing engineered probiotic therapeutics to treat inborn errors of metabolism and has a product candidate in a Phase 1 trial for the treatment of urea cycle disorders, as well as a Phase 1/2 program for the treatment of PKU. Finally, Agios Pharmaceuticals, Inc. declared that they are in the early discovery stage with a small molecule approach to PKU treatment. In addition, we anticipate competing with the largest biopharmaceutical companies in the world, such as Novartis AG, Gilead Sciences, Inc., Amgen, Inc., F. Hoffman-La Roche AG (Roche), Johnson & Johnson, and Pfizer Inc., which are all currently conducting research in cellular therapies.

Government regulation

Government authorities in the United States at the federal, state and local level and in other countries regulate, among other things, the research, development, testing, manufacture, quality control, approval, labeling, packaging, storage, record-keeping, promotion, advertising, distribution, post-approval monitoring and reporting, marketing and export and import of drug and biological products, such RTX-134 and RTX-240, and any future product candidates. Generally, before a new drug or biologic can be marketed, considerable data demonstrating its quality, safety and efficacy must be obtained, organized into a format specific for each regulatory authority, submitted for review and approved by the regulatory authority.

U.S. biological product development

In the United States, the FDA regulates biological products under the Federal Food, Drug, and Cosmetic Act, or FDCA, the Public Health Service Act, or PHSA, and regulations thereunder. Biologics are also subject to other federal, state and local statutes and regulations. The process of obtaining regulatory approvals and the subsequent compliance with appropriate federal, state and local statutes and regulations requires the expenditure of substantial time and financial resources. Failure to comply with the applicable U.S. requirements at any time during the product development process, approval process or post-market may subject an applicant to administrative or judicial sanctions. These sanctions could include, among other actions, the FDA's refusal to approve pending applications, withdrawal of an approval, a clinical hold, untitled or warning letters, product recalls or market withdrawals, product seizures, total or partial suspension of production or distribution, injunctions, fines, refusals of government contracts, restitution, disgorgement and civil or criminal penalties. Any agency or judicial enforcement action could have a material adverse effect on us.

The FDA categorizes human cell- or tissue-based products as either minimally manipulated or more than minimally manipulated, and has determined that more than minimally manipulated products must be approved by the FDA through the biologics license application, or BLA, process before they may be legally marketed in the United States. The process required by the FDA before a biologic may be marketed in the United States generally involves the following:

- completion of extensive preclinical studies in accordance with applicable regulations, including studies conducted in accordance with good laboratory practice, or GLP, requirements;
- submission to the FDA of an IND, which must become effective before human clinical trials may begin;
- approval by an institutional review board, or IRB, or independent ethics committee at each clinical trial site before each trial may be initiated;
- performance of adequate and well-controlled human clinical trials in accordance with applicable IND regulations, good clinical practice, or GCP, requirements and other clinical trial-related regulations to establish the safety and efficacy of the investigational product for each proposed indication;
- submission to the FDA of a BLA;

- a determination by the FDA within 60 days of its receipt of a BLA to accept the filing for review;
- satisfactory completion of an FDA pre-approval inspection of the manufacturing facility or facilities where the biologic will be produced to assess compliance with cGMP requirements and, if applicable, current Good Tissue Practices, or cGTP, to assure that the facilities, methods and controls are adequate to preserve the drug or biologic's identity, strength, quality and purity;
- potential FDA audit of the nonclinical and clinical trial sites that generated the data in support of the BLA; and
- FDA review and approval of the BLA, including consideration of the views of any FDA advisory committee, prior to any commercial marketing or sale of the biological product in the United States.

The preclinical and clinical testing and approval process requires substantial time, effort and financial resources, and we cannot be certain that any approvals for RTX-134 and RTX-240 and any future product candidates will be granted on a timely basis, or at all.

Preclinical studies and IND

Preclinical studies include laboratory evaluation of product chemistry and formulation, as well as *in vitro* and animal studies to assess safety and in some cases to establish a rationale for therapeutic use. The conduct of preclinical studies is subject to federal regulations and requirements, including GLP regulations for safety and toxicology studies.

An IND is a request for authorization from the FDA to administer an investigational product to humans and must become effective before human clinical trials may begin. An IND sponsor must submit the results of the preclinical tests, together with manufacturing information, analytical data, any available clinical data or literature and plans for clinical studies, among other things, to the FDA as part of an IND. An IND automatically becomes effective 30 days after receipt by the FDA, unless the FDA raises concerns or questions related to one or more proposed clinical trials and places the trial on clinical hold before such time. In such a case, the IND sponsor and the FDA must resolve any outstanding concerns before the clinical trial can begin. If the FDA's concerns are not resolved, submission of an IND may not result in the FDA allowing clinical trials to commence. With gene therapy protocols, if the FDA allows the IND to proceed, but a RAC decides that full public review of the protocol is warranted, the FDA will request at the completion of its IND review that sponsors delay initiation of the protocol until after completion of the RAC review process.

In addition to the IND submission process, sponsors of certain clinical studies of cells containing recombinant or synthetic nucleic acid molecules, including human gene transfer studies, must comply with the NIH's Guidelines for Research Involving Recombinant or Synthetic Nucleic Acid Molecules, or NIH Guidelines. The NIH Guidelines set forth the principles and requirements for NIH and institutional oversight of research with recombinant or synthetic nucleic acid molecules, including the standards for investigators and institutions to follow to ensure the safe handling and containment of such molecules. In April 2016, modifications to the NIH Guidelines went into effect, pursuant to which only a subset of human gene transfer protocols are subject to review by the RAC. Specifically, under the modified NIH Guidelines, RAC review of the protocol will be required only in exceptional cases where an oversight body such as an Institutional Biosafety Committee, or IBC, which provides local review and oversight of research utilizing recombinant or synthetic nucleic acid molecules, or an IRB determines that the protocol would significantly benefit from RAC review, and the protocol (a) uses a new vector, genetic material, or delivery methodology that represents a first-in-human experience and thus presents an unknown risk, and/or (b) relies on preclinical safety data that were obtained using a new preclinical model system of unknown and unconfirmed value, and/or (c) involves a proposed vector, gene construct, or method of delivery associated with possible toxicities that are not widely known and that may render it difficult for oversight bodies to evaluate the protocol rigorously. The RAC review proceedings are public, and reports are posted publicly to the website for the NIH's Office of Biotechnology Activities. Although compliance with the NIH Guidelines is mandatory for research conducted at or sponsored by institutions receiving NIH funding of recombinant or synthetic nucleic acid molecule research, many companies and other institutions not otherwise subject to the NIH Guidelines voluntarily follow them. Independent of RAC review, the NIH Guidelines also require all human gene transfer protocols subject to the NIH Guidelines to be registered with NIH, with limited exemptions. A study subject to the NIH Guidelines may not begin until the IBC approves the protocol, and the IBC cannot approve the

protocol until confirmation from the NIH that such registration is complete. In the event that RAC review is warranted, the protocol registration process cannot be completed until RAC review has taken place.

Clinical trials

The clinical stage of development involves the administration of the investigational product to healthy volunteers or patients under the supervision of qualified investigators, generally physicians not employed by or under the trial sponsor's control, in accordance with GCP requirements, which include the requirement that all research subjects provide their informed consent for their participation in any clinical trial. Clinical trials are conducted under protocols detailing, among other things, the objectives of the clinical trial, dosing procedures, subject selection and exclusion criteria and the parameters to be used to monitor subject safety and assess efficacy. Each protocol, and any subsequent amendments to the protocol, must be submitted to the FDA as part of the IND. Furthermore, each clinical trial must be reviewed and approved by an IRB for each institution at which the clinical trial will be conducted to ensure that the risks to individuals participating in the clinical trials are minimized and are reasonable in relation to anticipated benefits. The IRB also approves the informed consent form that must be provided to each clinical trial subject or his or her legal representative, and must monitor the clinical trial until completed. There also are requirements governing the reporting of ongoing clinical trials and completed clinical trial results to public registries.

A sponsor who wishes to conduct a clinical trial outside of the United States may, but need not, obtain FDA authorization to conduct the clinical trial under an IND. If a foreign clinical trial is not conducted under an IND, the sponsor may submit data from the clinical trial to the FDA in support of a BLA or NDA. The FDA will accept a well-designed and well-conducted foreign clinical trial not conducted under an IND if the trial was conducted in accordance with GCP requirements, and the FDA is able to validate the data through an onsite inspection if deemed necessary.

Clinical trials generally are conducted in three sequential phases, known as Phase 1, Phase 2 and Phase 3, and may overlap.

- Phase 1 clinical trials generally involve a small number of healthy volunteers or disease-affected patients who are initially exposed to a single dose and then multiple doses of the product candidate. The primary purpose of these clinical trials is to assess the metabolism, pharmacologic action, side effect tolerability and safety of the drug.

- Phase 2 clinical trials involve studies in disease-affected patients to determine the dose required to produce the desired benefits. At the same time, safety and further pharmacokinetic and pharmacodynamic information is collected, possible adverse effects and safety risks are identified and a preliminary evaluation of efficacy is conducted.

- Phase 3 clinical trials generally involve a large number of patients at multiple sites and are designed to provide the data necessary to demonstrate the effectiveness of the product for its intended use, its safety in use and to establish the overall benefit and risk relationship of the product and provide an adequate basis for product labeling.

Post-approval trials, sometimes referred to as Phase 4 clinical trials, may be conducted after initial marketing approval. These trials are used to gain additional experience from the treatment of patients in the intended therapeutic indication. In certain instances, the FDA may mandate the performance of Phase 4 clinical trials as a condition of approval of a BLA.

Progress reports detailing the results of the clinical trials, among other information, must be submitted at least annually to the FDA and written IND safety reports must be submitted to the FDA and the investigators for serious and unexpected suspected adverse events, findings from other studies or animal or *in vitro* testing that suggest a significant risk for human subjects and any clinically important increase in the rate 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, if at all. 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 or patients are being exposed to an unacceptable health risk. Similarly, an IRB can suspend or

terminate approval of a clinical trial at its institution if the clinical trial is not being conducted in accordance with the IRB's requirements or if the drug or biologic has been associated with unexpected serious harm to patients. Additionally, some clinical trials are overseen by an independent group of qualified experts organized by the clinical trial sponsor, known as a data safety monitoring board or committee. This group provides authorization for whether a trial may move forward at designated check points based on access to certain data from the trial. Concurrent with clinical trials, companies usually complete additional animal studies and also must develop additional information about the chemistry and physical characteristics of the drug or biologic as well as finalize a process for manufacturing the product in commercial quantities in accordance with cGMP requirements. The manufacturing process must be capable of consistently producing quality batches of the product and companies must develop methods for testing the identity, strength, quality and purity of the final product, among other things. Additionally, appropriate packaging must be selected and tested and stability studies must be conducted to demonstrate that the product candidates do not undergo unacceptable deterioration over their shelf life.

BLA and FDA review process

Following completion of the clinical trials, data are analyzed to assess whether the investigational product is safe and effective for the proposed indicated use or uses. The results of preclinical studies and clinical trials are then submitted to the FDA as part of a BLA, a request for approval to market the biological product for one or more specified indications, along with proposed labeling, chemistry and manufacturing information to ensure product quality and other relevant data. The application may include both negative and ambiguous results of preclinical studies and clinical trials, as well as positive findings. Data may come from company-sponsored clinical trials intended to test the safety and efficacy of a product's use or from a number of alternative sources, including studies initiated by investigators. To support marketing approval, the data submitted must be sufficient in quality and quantity to establish the safety and efficacy of the investigational product to the satisfaction of FDA. FDA approval of a BLA must be obtained before a biologic may be marketed in the United States.

Under the Prescription Drug User Fee Act, or PDUFA, as amended, each BLA must be accompanied by a user fee. The FDA adjusts the PDUFA user fees on an annual basis. According to the FDA's fee schedule, effective through December 31, 2018, the user fee for an application requiring clinical data, such as a BLA or NDA, is $2,421,495. The sponsor of an approved BLA is also subject to an annual prescription drug program fee, which for fiscal year 2018 is $304,162. Fee waivers or reductions are available in certain circumstances, including a waiver of the application fee for the first application filed by a small business. Additionally, no user fees are assessed on BLAs for products designated as orphan drugs, unless the product also includes a non-orphan indication.

The FDA reviews all submitted BLAs before it accepts them for filing, and may request additional information rather than accepting the BLA for filing. The FDA must make a decision on accepting a BLA for filing within 60 days of receipt. Once the submission is accepted for filing, the FDA begins an in-depth review of the BLA. Under the goals and policies agreed to by the FDA under PDUFA, the FDA has ten months, from the filing date, in which to complete its initial review of an original BLA and respond to the applicant, and six months from the filing date of an original BLA designated for priority review. The FDA does not always meet its PDUFA goal dates for standard and priority BLAs, and the review process is often extended by FDA requests for additional information or clarification.

Before approving a BLA, the FDA will conduct a pre-approval inspection of the manufacturing facilities for the new product to determine whether they comply with cGMP requirements and, if applicable, cGTP requirements. These are FDA regulations that govern the methods used in, and the facilities and controls used for, the manufacture of human cells, tissues, and cellular and tissue based products, or HCT/Ps, which are human cells or tissue intended for implantation, transplant, infusion, or transfer into a human recipient. The primary intent of the cGTP requirements is to ensure that cell and tissue based products are manufactured in a manner designed to prevent the introduction, transmission and spread of communicable disease. FDA regulations also require tissue establishments to register and list their products with the FDA and, when applicable, to evaluate donors through screening and testing. The FDA will not approve the product unless it determines that the manufacturing processes and facilities are in compliance with cGMP and cGTP requirements and adequate to assure consistent production of the product within required specifications. The FDA also may audit data from clinical trials to ensure compliance with GCP requirements. Additionally, the FDA may refer applications for novel products or products which present difficult questions of safety or efficacy to an advisory committee, typically a panel that includes clinicians and other experts, for review, evaluation and a recommendation as

to whether the application should be approved and under what conditions, if any. The FDA is not bound by recommendations of an advisory committee, but it considers such recommendations when making decisions on approval. The FDA likely will reanalyze the clinical trial data as part of the review process, which could result in extensive discussions between the FDA and the applicant during the process.

After the FDA evaluates a BLA, it will issue an approval letter or a Complete Response Letter, or CRL. An approval letter authorizes commercial marketing of the drug or biologic with specific prescribing information for specific indications. A CRL indicates that the review cycle of the application is complete and the application will not be approved in its present form. A CRL usually describes all of the specific deficiencies in the BLA identified by the FDA. The CRL may require additional clinical data, additional pivotal Phase 3 clinical trial(s) or other significant and time-consuming requirements related to clinical trials, preclinical studies or manufacturing. If a CRL is issued, the applicant may either resubmit the BLA, addressing all of the deficiencies identified in the letter, or withdraw the application. Even if such data and information are submitted, the FDA may decide that the BLA does not satisfy the criteria for approval. Data obtained from clinical trials are not always conclusive and the FDA may interpret data differently than we interpret the same data.

If regulatory approval of a product is granted, such approval will be granted for particular indications and may entail limitations on the indicated uses for which such product may be marketed. For example, the FDA may approve the BLA with a Risk Evaluation and Mitigation Strategy, or REMS, to ensure the benefits of the product outweigh its risks. A REMS is a safety strategy to manage a known or potential serious risk associated with a medicine and to enable patients to have continued access to such medicines by managing their safe use, and could include medication guides, physician communication plans or elements to assure safe use, such as restricted distribution methods, patient registries and other risk minimization tools. The FDA also may condition approval on, among other things, changes to proposed labeling or the development of adequate controls and specifications. Once approved, the FDA may withdraw the product approval if compliance with pre- and post-marketing requirements is not maintained or if problems occur after the product reaches the marketplace. The FDA may require one or more Phase 4 post-market studies or surveillance to further assess and monitor the product's safety and effectiveness after commercialization, and may limit further marketing of the product based on the results of these post-marketing studies. In addition, new government requirements, including those resulting from new legislation, may be established, or the FDA's policies may change, which could impact the timeline for regulatory approval or otherwise impact ongoing development programs.

Orphan drug designation

Under the Orphan Drug Act, the FDA may grant orphan drug designation to a biological product intended to treat a rare disease or condition, which is generally a disease or condition that affects fewer than 200,000 individuals in the United States, or more than 200,000 individuals in the United States and for which there is no reasonable expectation that the cost of developing and making the product available in the United States for this type of disease or condition will be recovered from sales of the product.

Orphan drug designation must be requested before submitting a BLA. After the FDA grants orphan drug designation, the identity of the therapeutic agent and its potential orphan use are disclosed publicly by the FDA. Orphan drug designation does not convey any advantage in or shorten the duration of the regulatory review and approval process.

If a product that has orphan drug designation subsequently receives the first FDA approval for the disease or condition for which it has such designation, the product is entitled to orphan drug exclusivity, which means that the FDA may not approve any other applications to market the same drug for the same indication for seven years from the date of such approval, except in limited circumstances. A product will not be considered the "same drug" if it is clinically superior to a product that has orphan drug exclusivity. Moreover, competitors may receive approval of either a different product for the same indication or the same product for a different indication, but which could be used off-label in the orphan indication. Orphan drug exclusivity also could block the approval of one of our products for seven years if a competitor obtains approval before we do for the same product, as defined by the FDA, for the same indication we are seeking approval, or if our product is determined to be contained within the scope of the competitor's product for the same indication or disease. If one of our products designated as an orphan drug receives marketing approval for an indication broader than that which is designated, it may not be entitled to orphan drug exclusivity.

Expedited development and review programs

The FDA has several programs that are intended to expedite or facilitate the process for reviewing new drugs and biologics that meet certain criteria. Specifically, new biologics are eligible for fast track designation if they are intended to treat a serious or life-threatening condition and preclinical or clinical data demonstrate the potential to address unmet medical needs for the condition. Fast track designation applies to both the product and the specific indication for which it is being studied. The sponsor can request the FDA to designate the product for fast track status any time before receiving BLA approval, but ideally no later than the pre-BLA meeting.

Any product submitted to the FDA for marketing, including under a fast track program, may be eligible for other types of FDA programs intended to expedite development and review, such as priority review and accelerated approval. Any product is eligible for priority review if it treats a serious or life-threatening condition and, if approved, would provide a significant improvement in safety and effectiveness compared to available therapies. The FDA will attempt to direct additional resources to the evaluation of an application for a new drug or biologic designated for priority review in an effort to facilitate the review.

A product may also be eligible for accelerated approval if it treats a serious or life-threatening condition and generally provides a meaningful advantage over available therapies. In addition, it must demonstrate an effect on a surrogate endpoint that is reasonably likely to predict clinical benefit or on a clinical endpoint that can be measured earlier than irreversible morbidity or mortality, or IMM, that is reasonably likely to predict an effect on IMM or other clinical benefit. As a condition of approval, the FDA may require that a sponsor of a drug or biologic receiving accelerated approval perform adequate and well-controlled post-marketing clinical trials. If the FDA concludes that a drug or biologic shown to be effective can be safely used only if distribution or use is restricted, it will require such post-marketing restrictions, as it deems necessary to assure safe use of the product.

Additionally, a drug or biologic may be eligible for designation as a breakthrough therapy if the product is intended, alone or in combination with one or more other drugs or biologics, to treat a serious or life-threatening condition and preliminary clinical evidence indicates that the product may demonstrate substantial improvement over currently approved therapies on one or more clinically significant endpoints. The benefits of breakthrough therapy designation include the same benefits as fast track designation, plus intensive interaction and guidance from the FDA. The breakthrough therapy designation is a distinct status from both accelerated approval and priority review, but these can also be granted to the same product candidate if the relevant criteria are met. The FDA must take certain actions, such as holding timely meetings and providing advice, intended to expedite the development and review of an application for approval of a breakthrough therapy. All requests for breakthrough therapy designation will be reviewed within 60 days of receipt, and FDA will either grant or deny the request.

Fast track designation, priority review, accelerated approval and breakthrough therapy designation do not change the standards for approval, but may expedite the development or approval process.

Regenerative medicine advanced therapy designation

As part of the 21st Century Cures Act, Congress recently amended the FDCA to create an accelerated approval pathway for certain regenerative medicine therapies, which include cell therapies, therapeutic tissue engineering products, human cell and tissue products, and combination products using any such therapies or products. Regenerative medicine therapies do not include those human cells, tissues and cellular and tissue based products regulated solely under section 361 of the Public Health Service Act and 21 CFR Part 1271. The new program is intended to facilitate efficient development and expedite review of RMATs, which are intended to treat, modify, reverse, or cure a serious or life-threatening disease or condition.

A sponsor may request that the FDA designate a drug as an RMAT concurrently with or at any time after submission of an IND. The FDA has 60 calendar days to determine whether the drug meets the criteria, including whether there is preliminary clinical evidence indicating that the product has the potential to address unmet medical needs for a serious or life-threatening disease or condition. The FDA generally expects preliminary clinical evidence to be obtained from clinical investigations specifically conducted to assess the effects of the therapy on a serious condition, which could

include well-designed retrospective studies or clinical case series, as appropriate, but the RMAT designation does not require evidence to indicate that the drug may offer a substantial improvement over existing therapies. Advantages of RMAT designation include all of the benefits of the fast track and breakthrough therapy designation programs, including early interactions with sponsors. In addition, a product that receives RMAT designation may be eligible for priority review, and the FDA may grant accelerated approval to products that have RMAT designation based on (1) previously agreed-upon surrogate or intermediate endpoints that are reasonably likely to predict long-term clinical benefit; or (2) reliance upon data obtained from a meaningful number of sites, including through expansion to additional sites, as appropriate. Another benefit of RMAT designation is that may enable to the sponsor to meet post-approval requirements beyond the completion of traditional confirmatory clinical trials. The FDA has indicated that post-approval requirements for RMATs receiving accelerated approval can potentially be met through:

- Clinical evidence, clinical studies, patient registries or other sources of real world evidence, such as electronic health records;
- The collection of larger confirmatory data sets; or
- Post-approval monitoring of all patients treated with such therapy prior to approval of the therapy.

As with breakthrough designation, an RMAT designation is not the same as an approval and does not change the statutory standards for demonstration of safety and effectiveness needed for marketing approval.

Pediatric information

Under the Pediatric Research Equity Act, or PREA, certain BLAs and certain supplements to a BLA must contain data to assess the safety and efficacy of the drug for the claimed indications in all relevant pediatric subpopulations and to support dosing and administration for each pediatric subpopulation for which the product is safe and effective. The FDA may grant deferrals for submission of pediatric data or full or partial waivers. The Food and Drug Administration Safety and Innovation Act amended the FDCA to require that a sponsor who is planning to submit a marketing application for a drug that includes a new active ingredient, new indication, new dosage form, new dosing regimen or new route of administration submit an initial Pediatric Study Plan, or PSP, within 60 days of an end-of-Phase 2 meeting or, if there is no such meeting, as early as practicable before the initiation of the Phase 3 or Phase 2/3 trial. The initial PSP must include an outline of the pediatric trial or trials that the sponsor plans to conduct, including trial objectives and design, age groups, relevant endpoints and statistical approach, or a justification for not including such detailed information, and any request for a deferral of pediatric assessments or a full or partial waiver of the requirement to provide data from pediatric studies along with supporting information. The FDA and the sponsor must reach an agreement on the PSP. A sponsor can submit amendments to an agreed-upon initial PSP at any time if changes to the pediatric plan need to be considered based on data collected from preclinical studies, early-phase clinical trials and/or other clinical development programs.

Post-marketing requirements

Following approval of a new product, the manufacturer and the approved product are subject to continuing regulation by the FDA, including, among other things, monitoring and record-keeping activities, reporting of adverse experiences, complying with promotion and advertising requirements, which include restrictions on promoting drugs for unapproved uses or patient populations (known as “off-label use”) and limitations on industry-sponsored scientific and educational activities. Although physicians may prescribe legally available drugs for off-label uses, manufacturers may not market or promote such uses. Prescription drug promotional materials must be submitted to the FDA in conjunction with their first use. Further, if there are any modifications to the drug or biologic, including changes in indications, labeling or manufacturing processes or facilities, the applicant may be required to submit and obtain FDA approval of a new BLA or BLA supplement, which may require the development of additional data or preclinical studies and clinical trials.

The FDA may also place other conditions on approvals including the requirement for a Risk Evaluation and Mitigation Strategy, or REMS, to assure the safe use of the product. If the FDA concludes a REMS is needed, the sponsor of the BLA must submit a proposed REMS. The FDA will not approve the BLA without an approved REMS, if required. A

REMS could include medication guides, physician communication plans or elements to assure safe use, such as restricted distribution methods, patient registries and other risk minimization tools. Any of these limitations on approval or marketing could restrict the commercial promotion, distribution, prescription or dispensing of products. Product approvals may be withdrawn for non-compliance with regulatory standards or if problems occur following initial marketing.

FDA regulations require that biological products be manufactured in specific approved facilities and in accordance with cGMP regulations and, in some cases, cGTP regulations. We rely, and expect to continue to rely, on third parties for the production of clinical and commercial quantities of our products in accordance with cGMP and cGTP regulations. These manufacturers must comply with cGMP and cGTP regulations that require, among other things, quality control and quality assurance, the maintenance of records and documentation and the obligation to investigate and correct any deviations from cGMP or cGTP. Manufacturers and other entities involved in the manufacture and distribution of approved drugs or biologics are required to register their establishments with the FDA and certain state agencies, and are subject to periodic unannounced inspections by the FDA and certain state agencies for compliance with cGMP and, if applicable, cGTP requirements and other laws. Accordingly, manufacturers must continue to expend time, money and effort in the area of production and quality control to maintain cGMP and cGTP compliance. Other post-approval requirements applicable to biological products, include reporting of cGMP deviations that may affect the identity, potency, purity and overall safety of a distributed product, record-keeping requirements, reporting of adverse effects, reporting updated safety and efficacy information, and complying with electronic record and signature requirements.

After a BLA is approved, the product also may be subject to official lot release. As part of the manufacturing process, the manufacturer is required to perform certain tests on each lot of the product before it is released for distribution. If the product is subject to official release by the FDA, the manufacturer submits samples of each lot of product to the FDA together with a release protocol showing a summary of the history of manufacture of the lot and the results of all of the manufacturer's tests performed on the lot. The FDA also may perform certain confirmatory tests on lots of some products, such as viral vaccines, before releasing the lots for distribution by the manufacturer. In addition, the FDA conducts laboratory research related to the regulatory standards on the safety, purity, potency, and effectiveness of biological products.

To help reduce the increased risk of the introduction of adventitious agents, the PHS Act emphasizes the importance of manufacturing controls for products whose attributes cannot be precisely defined. The PHS Act also provides authority to the FDA to immediately suspend biologics licenses in situations where there exists a danger to public health, to prepare or procure products in the event of shortages and critical public health needs, and to authorize the creation and enforcement of regulations to prevent the introduction or spread of communicable diseases within the United States.

Discovery of previously unknown problems or the failure to comply with the applicable regulatory requirements may result in restrictions on the marketing of a product or withdrawal of the product from the market as well as possible civil or criminal sanctions. Failure to comply with the applicable U.S. requirements at any time during the product development process, approval process or after approval, may subject an applicant or manufacturer to administrative or judicial civil or criminal sanctions and adverse publicity. FDA sanctions could include refusal to approve pending applications, withdrawal of an approval, clinical hold, warning or untitled letters, product recalls, product seizures, total or partial suspension of production or distribution, injunctions, fines, refusals of government contracts, mandated corrective advertising or communications with doctors, debarment, restitution, disgorgement of profits, or civil or criminal penalties. Any agency or judicial enforcement action could have a material adverse effect on us.

Biological product manufacturers and other entities involved in the manufacture and distribution of approved biological products are required to register their establishments with the FDA and certain state agencies, and are subject to periodic unannounced inspections by the FDA and certain state agencies for compliance with cGMP and, if applicable, cGTP requirements and other laws. Accordingly, manufacturers must continue to expend time, money, and effort in the area of production and quality control to maintain cGMP compliance. Discovery of problems with a product after approval may result in restrictions on a product, manufacturer, or holder of an approved BLA, including withdrawal of the product from the market. In addition, changes to the manufacturing process or facility generally require prior FDA approval before being implemented and other types of changes to the approved product, such as adding new indications and additional labeling claims, are also subject to further FDA review and approval.

U.S. patent term restoration and marketing exclusivity

Depending upon the timing, duration and specifics of FDA approval of RTX-134, RTX-240 and RTX-224 and any future product candidates, some of our U.S. patents may be eligible for limited patent term extension under the Drug Price Competition and Patent Term Restoration Act of 1984, commonly referred to as the Hatch-Waxman Amendments. The Hatch-Waxman Amendments permit restoration of the patent term of up to five years as compensation for patent term lost during product development and FDA regulatory review process. Patent-term restoration, however, cannot extend the remaining term of a patent beyond a total of 14 years from the product's approval date. The patent-term restoration period is generally one-half the time between the effective date of an IND and the submission date of a BLA plus the time between the submission date of a BLA and the approval of that application, except that the review period is reduced by any time during which the applicant failed to exercise due diligence. Only one patent applicable to an approved product is eligible for the extension and the application for the extension must be submitted prior to the expiration of the patent. The United States Patent and Trademark Office, in consultation with the FDA, reviews and approves the application for any patent term extension or restoration. In the future, we may apply for restoration of patent term for our currently owned or licensed patents to add patent life beyond its current expiration date, depending on the expected length of the clinical trials and other factors involved in the filing of the relevant BLA.

An abbreviated approval pathway for biological products shown to be similar to, or interchangeable with, an FDA-licensed reference biological product was created by the Biologics Price Competition and Innovation Act of 2009 as part of the Patient Protection and Affordable Care Act, as amended by the Health Care and Education Reconciliation Act of 2010, or the ACA. This amendment to the PHSA, in part, attempts to minimize duplicative testing. Bio similarity, which requires that the biological product be highly similar to the reference product notwithstanding minor differences in clinically inactive components and that there be no clinically meaningful differences between the product and the reference product in terms of safety, purity and potency, can be shown through analytical studies, animal studies and a clinical trial or trials. Interchangeability requires that a biological product be biosimilar to the reference product and that the product can be expected to produce the same clinical results as the reference product in any given patient and, for products administered multiple times to an individual, that the product and the reference product may be alternated or switched after one has been previously administered without increasing safety risks or risks of diminished efficacy relative to exclusive use of the reference biological product without such alternation or switch. Complexities associated with the larger, and often more complex, structure of biological products as compared to small molecule drugs, as well as the processes by which such products are manufactured, pose significant hurdles to implementation that are still being worked out by the FDA.

A reference biological product is granted four and twelve year exclusivity periods from the time of first licensure of the product. The FDA will not accept an application for a biosimilar or interchangeable product based on the reference biological product until four years after the date of first licensure of the reference product, and the FDA will not approve an application for a biosimilar or interchangeable product based on the reference biological product until twelve years after the date of first licensure of the reference product. "First licensure" typically means the initial date the particular product at issue was licensed in the United States. Date of first licensure does not include the date of licensure of (and a new period of exclusivity is not available for) a biological product if the licensure is for a supplement for the biological product or for a subsequent application by the same sponsor or manufacturer of the biological product (or licensor, predecessor in interest, or other related entity) for a change (not including a modification to the structure of the biological product) that results in a new indication, route of administration, dosing schedule, dosage form, delivery system, delivery device or strength, or for a modification to the structure of the biological product that does not result in a change in safety, purity or potency. Therefore, one must determine whether a new product includes a modification to the structure of a previously licensed product that results in a change in safety, purity or potency to assess whether the licensure of the new product is a first licensure that triggers its own period of exclusivity. Whether a subsequent application, if approved, warrants exclusivity as the "first licensure" of a biological product is determined on a case-by-case basis with data submitted by the sponsor.

Pediatric exclusivity is another type of regulatory market exclusivity in the United States. Pediatric exclusivity, if granted, adds six months to existing regulatory exclusivity periods. This six-month exclusivity may be granted based on the voluntary completion of a pediatric trial in accordance with an FDA-issued "Written Request" for such a trial.

European Union drug development

In the E.U., our future products also may be subject to extensive regulatory requirements. As in the United States, medicinal products can be marketed only if a marketing authorization from the competent regulatory agencies has been obtained.

Similar to the United States, the various phases of preclinical and clinical research in the E.U. are subject to significant regulatory controls. Although the E.U. Clinical Trials Directive 2001/20/EC has sought to harmonize the E.U. clinical trials regulatory framework, setting out common rules for the control and authorization of clinical trials in the E.U., the E.U. Member States have transposed and applied the provisions of the Directive differently. This has led to significant variations in the member state regimes. Under the current regime, before a clinical trial can be initiated it must be approved in each of the E.U. countries where the trial is to be conducted by two distinct bodies: the National Competent Authority, or NCA, and one or more Ethics Committees, or ECs.

The E.U. clinical trials legislation currently is undergoing a transition process mainly aimed at harmonizing and streamlining clinical trial authorization, simplifying adverse event reporting procedures, improving the supervision of clinical trials and increasing their transparency. Recently enacted Clinical Trials Regulation E.U. No 536/2014 ensures that the rules for conducting clinical trials in the E.U. will be identical.

European Union drug marketing

Much like the Anti-Kickback Statute prohibition in the United States discussed below, 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 also prohibited in the European Union. The provision of benefits or advantages to physicians is governed by the national anti-bribery laws of E.U. Member States, such as the UK Bribery Act 2010. Infringement of these laws could result in substantial fines and imprisonment.

Payments made to physicians in certain E.U. Member States 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 the regulatory authorities of the individual E.U. Member States. These requirements are provided in the national laws, industry codes or professional codes of conduct, applicable in the E.U. Member States. Failure to comply with these requirements could result in reputational risk, public reprimands, administrative penalties, fines or imprisonment.

European Union drug review and approval

In the European Economic Area, or EEA, which is comprised of all 28 E.U. Member States (except Croatia) and also Norway, Iceland and Liechtenstein, medicinal products can only be commercialized after obtaining a Marketing Authorization, or MA. There are two types of marketing authorizations.

- The Community MA is issued by the European Commission through the Centralized Procedure, based on the opinion of the Committee for Medicinal Products for Human Use of the European Medicines Agency, or EMA, and is valid throughout the entire territory of the EEA. The Centralized Procedure is mandatory for certain types of products, such as biotechnology medicinal products, orphan medicinal products, advanced-therapy medicines, such as gene therapy, somatic cell therapy or tissue-engineered medicines and medicinal products containing a new active substance indicated for the treatment of HIV, AIDS, cancer, neurodegenerative disorders, diabetes, autoimmune and other immune dysfunctions and viral diseases. The Centralized Procedure is optional for products containing a new active substance not yet authorized in the EEA, or for products that constitute a significant therapeutic, scientific or technical innovation or which are in the interest of public health in the E.U.

- National MAs, which are issued by the competent authorities of the Member States of the EEA and only cover their respective territory, are available for products not falling within the mandatory scope of the Centralized Procedure. Where a product has already been authorized for marketing in a Member State of the EEA, this National MA can be recognized in another Member States through the Mutual Recognition Procedure. If the product has not received a

National MA in any Member State at the time of application, it can be approved simultaneously in various Member States through the Decentralized Procedure. Under the Decentralized Procedure, an identical dossier is submitted to the competent authorities of each of the Member States in which the MA is sought, one of which is selected by the applicant as the Reference Member State, or RMS. The competent authority of the RMS prepares a draft assessment report, a draft summary of the product characteristics, or SPC, and a draft of the labeling and package leaflet, which are sent to the other Member States (referred to as the Member States Concerned) for their approval. If the Member States Concerned raise no objections, based on a potential serious risk to public health, to the assessment, SPC, labeling, or packaging proposed by the RMS, the product is subsequently granted a national MA in all the Member States (i.e., in the RMS and the Member States Concerned).

Under the above described procedures, before granting the MA, the EMA or the competent authorities of the Member States of the EEA make an assessment of the risk-benefit balance of the product on the basis of scientific criteria concerning its quality, safety and efficacy.

European Union new chemical entity exclusivity

In the E.U., new chemical entities, sometimes referred to as new active substances, qualify for eight years of data exclusivity upon marketing authorization and an additional two years of market exclusivity. The data exclusivity, if granted, prevents regulatory authorities in the E.U. from referencing the innovator's data to assess a generic application for eight years, after which generic marketing authorization can be submitted, and the innovator's data may be referenced, but not approved for two years. 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 determined to bring a significant clinical benefit in comparison with currently approved therapies.

European Union orphan drug designation and exclusivity

In the E.U., the EMA's Committee for Orphan Medicinal Products grants orphan drug designation to promote the development of products that are intended for the diagnosis, prevention or treatment of life-threatening or chronically debilitating conditions affecting not more than 5 in 10,000 persons in the E.U. community (or where it is unlikely that the development of the medicine would generate sufficient return to justify the investment) and for which no satisfactory method of diagnosis, prevention or treatment has been authorized (or, if a method exists, the product would be a significant benefit to those affected).

In the E.U., orphan drug designation entitles a party to financial incentives such as reduction of fees or fee waivers and ten years of market exclusivity is granted following medicinal product approval. This period may be reduced to six years if the orphan drug designation criteria are no longer met, including where it is shown that the product is sufficiently profitable not to justify maintenance of market exclusivity. Orphan drug designation must be requested before submitting an application for marketing approval. Orphan drug designation does not convey any advantage in, or shorten the duration of, the regulatory review and approval process.

European data collection

The collection and use of personal health data in the E.U. is governed by the provisions of the Data Protection Directive, and as of May 2018 the General Data Protection Regulation, or the GDPR. This directive imposes several requirements relating to the consent of the individuals to whom the personal data relates, the information provided to the individuals, notification of data processing obligations to the competent national data protection authorities and the security and confidentiality of the personal data. The Data Protection Directive and the GDPR also impose strict rules on the transfer of personal data out of the E.U. to the United States. Failure to comply with the requirements of the Data Protection Directive, the GDPR, and the related national data protection laws of the E.U. Member States may result in fines and other administrative penalties. The GDPR introduces new data protection requirements in the E.U. and substantial fines for breaches of the data protection rules. The GDPR regulations may impose additional responsibility and liability in relation to personal data that we process and we may be required to put in place additional mechanisms ensuring compliance with the new data protection rules. This may be onerous and adversely affect our business, financial

condition, results of operations and prospects. For more information related to GDPR, please see "Risk Factors—Risks related to government regulation—European data collection is governed by restrictive regulations governing the use, processing, and cross-border transfer of personal information."

Rest of the world regulation

For other countries outside of the E.U. and the United States, the requirements governing the conduct of clinical trials, product licensing, pricing and reimbursement vary from country to country. Additionally, the clinical trials must be conducted in accordance with GCP requirements and the applicable regulatory requirements and the ethical principles that have their origin in the Declaration of Helsinki.

If we fail to comply with applicable foreign regulatory requirements, we may be subject to, among other things, fines, suspension or withdrawal of regulatory approvals, product recalls, seizure of products, operating restrictions and criminal prosecution.

Additional laws and regulations governing international operations

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 the company 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 also may suspend or bar issuers from trading securities on U.S. exchanges for violations of the FCPA's accounting provisions.

Coverage and reimbursement

Successful commercialization of new drug and biologic products depends in part on the extent to which reimbursement for those drug and biologic products will be available from government health administration authorities, private health insurers and other organizations. These bodies decide which drug and biologic products they will pay for and establish reimbursement levels. The availability and extent of reimbursement by governmental and private payors is essential for most patients to be able to afford a drug or biologic product. Sales of drug and biologic products depend substantially, both domestically and abroad, on the extent to which the costs of these products are paid for by health maintenance,

managed care, pharmacy benefit and similar healthcare management organizations, or reimbursed by government health administration authorities, private health coverage insurers and other third-party payors.

In the United States, the important decisions about reimbursement for new drug and biologic products are made by the Centers for Medicare & Medicaid Services, or CMS, an agency within the U.S. Department of Health and Human Services, or HHS, as well as major health insurers. CMS decides whether and to what extent a new product will be covered and reimbursed under Medicare, and private payors tend to follow CMS to a substantial degree. However, no uniform policy of coverage and reimbursement for drug and biologic products exists among third-party payors and coverage and reimbursement levels for drug and biologic products can differ significantly from payor to payor.

The Medicare Prescription Drug, Improvement, and Modernization Act of 2003, also called the Medicare Modernization Act, or the MMA, established the Medicare Part D program to provide a voluntary prescription drug and biologic benefit to Medicare beneficiaries. Under Part D, Medicare beneficiaries may enroll in prescription drug plans offered by private entities that provide coverage of outpatient prescription drugs and biologics. Unlike Medicare Parts A and B, Part D coverage is not standardized. Part D prescription drug plan sponsors are not required to pay for all covered Part D drugs and biologics, and each drug plan can develop its own formulary that identifies which drugs and biologics it will cover, and at what tier or level. However, Part D prescription drug formularies must include products within each therapeutic category and class of covered Part D drugs, though not necessarily all the drugs and biologics in each category or class. Any formulary used by a Part D prescription drug plan must be developed and reviewed by a pharmacy and therapeutic committee. Government payment for some of the costs of prescription drugs and biologics may increase demand for products for which we obtain marketing approval. Any negotiated prices for any of our products covered by a Part D prescription drug plan will likely be lower than the prices we might otherwise obtain. Moreover, while the MMA applies only to drug benefits for Medicare beneficiaries, private payors often follow Medicare coverage policy and payment limitations in setting their own payment rates. Any reduction in payment that results from the MMA may result in a similar reduction in payments from non-governmental payors.

For a drug or biologic product to receive federal reimbursement under the Medicaid or Medicare Part B programs or to be sold directly to U.S. government agencies, the manufacturer must extend discounts to entities eligible to participate in the 340B drug pricing program. The required 340B discount on a given product is calculated based on the average manufacturer price, or AMP, and Medicaid rebate amounts reported by the manufacturer. As of 2010, the ACA expanded the types of entities eligible to receive discounted 340B pricing, although under the current state of the law these newly eligible entities (with the exception of children's hospitals) will not be eligible to receive discounted 340B pricing on orphan drugs. As 340B drug pricing is determined based on AMP and Medicaid rebate data, the revisions to the Medicaid rebate formula and AMP definition described above could cause the required 340B discount to increase. Further, on December 27, 2018, the District Court for the District of Columbia invalidated a recent reimbursement formula change instituted by CMS under the 340B program. It is unclear how this decision could affect covered hospitals who might purchase our products in the future, and affect the rates we may charge such facilities for our approved products. The American Recovery and Reinvestment Act of 2009 provides funding for the federal government to compare the effectiveness of different treatments for the same illness. The plan for the research was published in 2012 by HHS, the Agency for Healthcare Research and Quality and the National Institutes for Health, and periodic reports on the status of the research and related expenditures are made to Congress. Although the results of the comparative effectiveness studies are not intended to mandate coverage policies for public or private payors, it is not clear what effect, if any, the research will have on the sales of our product candidates. It is also possible that comparative effectiveness research demonstrating benefits in a competitor's drug could adversely affect the sales of our product candidates. If third-party payors do not consider our products to be cost-effective compared to other available therapies, they may not cover our products after approval as a benefit under their plans or, if they do, the level of payment may not be sufficient to allow us to sell our drugs on a profitable basis.

These current laws and state and federal healthcare reform measures that may be adopted in the future may result in additional reductions in Medicare and other healthcare funding and otherwise affect the prices we may obtain for any product candidates for which we may obtain regulatory approval or the frequency with which any such product candidate is prescribed or used.

Outside of the United States, the pricing of pharmaceutical products is subject to governmental control as part of national health systems in many countries. In general, the prices of drug and biologic products under such systems are substantially lower than in the United States. Other countries allow companies to fix their own prices for drug and biologic products, but monitor and control company profits. Efforts to control prices and utilization of pharmaceutical products and medical devices will likely continue as countries attempt to manage healthcare expenditures. Accordingly, in markets outside the United States the reimbursement for our products may be reduced compared with the United States.

Other healthcare laws

Healthcare providers, physicians and third party payors will play a primary role in the recommendation and prescription of any products for which we obtain marketing approval. Arrangements with third party payors, healthcare providers and physicians may expose a pharmaceutical or biologics manufacturer to broadly applicable fraud and abuse and other healthcare laws and regulations. In the United States, these laws include, without limitation, state and federal anti-kickback, false claims, physician transparency and patient data privacy and security laws and regulations, including but not limited to those described below:

- the federal Anti-Kickback Statute makes it illegal for any person, including a prescription drug or biologic manufacturer (or a party acting on its behalf) to knowingly and willfully solicit receive, offer or pay any remuneration (including any kickback, bribe or rebate), directly or indirectly, overtly or covertly, in cash or in kind, that is intended to induce or reward referrals including the purchase, recommendation, order or prescription of a particular drug for which payment may be made under a federal healthcare program, such as the Medicare and Medicaid programs. Violation of the statute does not require actual knowledge of the statute or specific intent to violate it. In addition, the government may assert that a claim, including items or services resulting from a violation of the federal Anti-Kickback Statute, constitutes a false or fraudulent claim for purposes of the False Claims Act;

- the federal civil and criminal false claims laws and civil monetary penalty laws, including the False Claims Act, impose criminal and civil penalties, including through civil "qui tam" or "whistleblower" actions, against individuals or entities for, among other things, knowingly presenting, or causing to be presented, claims for payment or approval from Medicare, Medicaid, or other federal healthcare programs that are false or fraudulent; knowingly making or causing a false statement material to a false or fraudulent claim or an obligation to pay money to the federal government; or knowingly concealing or knowingly and improperly avoiding or decreasing such an obligation. Similar to the federal Anti-Kickback Statute, a person or entity does not need to have actual knowledge of these statutes or specific intent to violate them in order to have committed a violation;

- the federal anti-inducement law, prohibits, among other things, the offering or giving of remuneration, which includes, without limitation, any transfer of items or services for free or for less than fair market value (with limited exceptions), to a Medicare or Medicaid beneficiary that the person knows or should know is likely to influence the beneficiary's selection of a particular supplier of items or services reimbursable by a federal or state governmental program;

- the federal Health Insurance Portability and Accountability Act of 1996, or HIPAA, created additional federal criminal statutes that prohibit knowingly and willfully executing, or attempting to execute, a scheme to defraud any healthcare benefit program or obtain, by means of false or fraudulent pretenses, representations, or promises, any of the money or property owned by, or under the custody or control of, any healthcare benefit program, regardless of the payor (e.g., public or private) and knowingly and willfully falsifying, concealing or covering up by any trick or device a material fact or making any materially false statements in connection with the delivery of, or payment for, healthcare benefits, items or services relating to healthcare matters;

- HIPAA, as amended by the Health Information Technology for Economic and Clinical Health Act of 2009, or HITECH, and their respective implementing regulations, impose requirements on certain covered healthcare providers, health plans and healthcare clearinghouses as well as their respective business associates that perform services for them that involve the use, or disclosure of, individually identifiable health information, relating to the privacy, security and transmission of individually identifiable health information;

- the U.S. Federal Food, Drug, and Cosmetic Act, or FDCA, which prohibits, among other things, the adulteration or misbranding of drugs, biologics and medical devices;

- the federal Physician Payments Sunshine Act, created under the ACA, and its implementing regulations, which require manufacturers of drugs, devices, biologicals and medical supplies for which payment is available under Medicare, Medicaid or the Children's Health Insurance Program to report annually to the HHS under the Open Payments Program, information related to payments or other transfers of value made to physicians and teaching hospitals, as well as ownership and investment interests held by physicians and their immediate family members; and

- analogous state and foreign laws and regulations, such as state and foreign anti-kickback, false claims, consumer protection and unfair competition laws which may apply to our business practices, including but not limited to, research, distribution, sales and marketing arrangements as well as submitting claims involving healthcare items or services reimbursed by any third-party payor, including commercial insurers; state laws that require pharmaceutical and biologics manufacturers to comply with the pharmaceutical industry's voluntary compliance guidelines and the relevant compliance guidance promulgated by the federal government that otherwise restricts payments that may be made to healthcare providers and other potential referral sources; state laws that require drug and biologic manufacturers to file reports with states regarding pricing and marketing information, such as the tracking and reporting of gifts, compensations and other remuneration and items of value provided to healthcare professionals and entities; state and local laws requiring the registration of pharmaceutical sales representatives; and state and foreign laws governing the privacy and security of health information in certain circumstances, many of which differ from each other in significant ways and may not have the same effect, thus complicating compliance efforts.

Because of the breadth of these laws and the narrowness of the statutory exceptions and regulatory safe harbors available, it is possible that some of our business activities could be subject to challenge under one or more of such laws. Efforts to ensure that business arrangements comply with applicable healthcare laws involve substantial costs. It is possible that governmental and enforcement authorities will conclude that our business practices do not comply with current or future statutes, regulations or case law interpreting applicable fraud and abuse or other healthcare laws and regulations. If any such actions are instituted against us, and we are not successful in defending ourselves or asserting our rights, those actions could have a significant impact on our business, including the imposition of civil, criminal and administrative penalties, damages, disgorgement, monetary fines, possible exclusion from participation in Medicare, Medicaid and other federal healthcare programs, integrity and oversight agreements to resolve allegations of non-compliance, contractual damages, reputational harm, diminished profits and future earnings, and curtailment of operations, any of which could adversely affect our ability to operate our business. In addition, commercialization of any of our products outside the United States will also likely be subject to foreign equivalents of the healthcare laws mentioned above, among other foreign laws.

Current and future healthcare reform legislation

In both the United States and certain foreign jurisdictions, there have been a number of legislative and regulatory changes to the healthcare system. In particular, in 2010 the ACA was enacted, which, among other things, increased the minimum Medicaid rebates owed by most manufacturers under the Medicaid Drug Rebate Program, extended the Medicaid Drug Rebate Program to utilization of prescriptions of individuals enrolled in Medicaid managed care organizations, subjected manufacturers to new annual fees and taxes for certain branded prescription drugs, and provided incentives to programs that increase the federal government's comparative effectiveness research.

There have been a number of significant changes to the ACA and its implementation. The Tax Cuts and Jobs Act of 2017, or Tax Act, includes a provision effective January 1, 2019 repealing the tax-based shared responsibility payment imposed by the ACA on certain individuals who fail to maintain qualifying health coverage for all or part of a year that is commonly referred to as the "individual mandate". On December 14, 2018, a U.S. District Court judge in the Northern District of Texas ruled that the individual mandate portion of the ACA is an essential and inseverable feature of the ACA, and therefore because the mandate was repealed as part of the Tax Cuts and Jobs Act, the remaining provisions of the ACA are invalid as well. The Trump administration and CMS have both stated that the ruling will have no immediate effect, and on December 30, 2018 the same judge issued an order staying the judgment pending appeal. It is unclear how

this decision and any subsequent appeals and other efforts to repeal and replace the ACA will impact the ACA and our business. Litigation and legislation over the ACA are likely to continue, with unpredictable and uncertain results. We continue to evaluate the effect that the Affordable Care Act and its possible repeal and replacement could have on our business.

Further, on January 20, 2017, President Trump signed an Executive Order directing federal agencies with authorities and responsibilities under the ACA to waive, defer, grant exemptions from, or delay the implementation of any provision of the ACA that would impose a fiscal 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 ACA. Several state Attorneys General filed suit to stop the administration from terminating the subsidies, but their request for a restraining order was denied by a federal judge in California on October 25, 2017. Moreover, on January 22, 2018, President Trump signed a continuing resolution on appropriations for fiscal year 2018 that delayed the implementation of certain ACA-mandated fees, including the so called “Cadillac” tax on certain high cost employer-sponsored insurance plans, the annual fee imposed on certain health insurance providers based on market share, and the medical device excise tax on non-exempt medical devices. The Bipartisan Budget Act of 2018 also amends the ACA, effective January 1, 2019, by increasing the point-of-sale discount that is owed by pharmaceutical manufacturers who participate in Medicare Part D and closing the coverage gap in most Medicare drug plans, commonly referred to as the “donut hole,” which will shift costs for name brand drugs away from Part D participants back to the manufacturers, which could have a negative effect on our profits in the event any of our products receive FDA approval and CMS reimbursement. Similarly, CMS recently proposed regulations that would give states greater flexibility in setting benchmarks for insurers in the individual and small group marketplaces, which may have the effect of relaxing the essential health benefits required under the ACA for plans sold through such marketplaces. On November 30, 2018, CMS announced a proposed rule that would amend the Medicare Advantage and Medicare Part D prescription drug benefit regulations to reduce out of pocket costs for plan enrollees and allow Medicare plans to negotiate lower rates for certain drugs. Among other things, the proposed rule changes would allow Medicare Advantage plans to use pre-authorization, or PA, and step therapy, or ST, for six protected classes of drugs, with certain exceptions, permit plans to implement PA and ST in Medicare Part B drugs, change the definition of "negotiated prices," and add a definition of "price concession" to the regulations. It is unclear whether these proposed changes we be accepted, and if so, what effect such changes will have on our business.

In addition, other legislative changes have been proposed and adopted in the United States since the ACA was enacted. In August 2011, the Budget Control Act of 2011, among other things, created measures for spending reductions by Congress. A Joint Select Committee on Deficit Reduction, tasked with recommending a targeted deficit reduction of at least $1.2 trillion for the years 2013 through 2021, was unable to reach required goals, thereby triggering the legislation’s automatic reduction to several government programs. This includes aggregate reductions of Medicare payments to providers of 2% per fiscal year, which went into effect in 2013, and, due to subsequent legislative amendments, will remain in effect through 2027 unless additional Congressional action is taken. The American Taxpayer Relief Act of 2012 further reduced Medicare payments to several providers, including hospitals and cancer treatment centers, and increased the statute of limitations period for the government to recover overpayments to providers from three to five years. Legislative and regulatory proposals, and enactment of laws, at the foreign, federal and state levels, directed at containing or lowering the cost of healthcare, will continue into the future.

Other Regulations

We are subject to numerous foreign, federal, state and local 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. In addition, our leasing and operation of real property may subject us to liability pursuant to certain U.S. environmental laws and regulations, under which current or previous owners or operators of real property and entities that disposed or arranged for the disposal of hazardous substances may be held strictly, jointly and severally liable for the cost of investigating or remediating contamination caused by hazardous substance releases, even if they did not know of and were not responsible for the releases.

Employees

As of February 28, 2019, we had 142 full-time employees, 42 of our employees have Ph.D. or M.D. degrees and 105 of our employees are engaged in research and development activities. None of our employees are represented by labor unions or covered by collective bargaining agreements. We consider our employee relations to be positive.

Facilities

Our corporate headquarters is located in approximately 85,000 square feet of office and laboratory space at in Cambridge, Massachusetts. The lease term for approximately 48,000 square feet commenced on January 28, 2019 and the lease term for the remaining 37,000 square feet is expected to commence in August 2019, following the completion of construction. The lease terms will expire eight and nine years from the commencement date of the 48,000 square feet and the remaining 37,000 square feet, respectively.

In July 2018, we purchased a 135,000 square foot manufacturing facility located in Smithfield, Rhode Island which is currently undergoing renovation and customization.

Legal proceedings

We are not currently a party to any material legal proceedings.

Corporate Information

Rubius was incorporated in April 2013 as VL26, Inc. under the laws of the State of Delaware. In January 2015, the Company changed its name to Rubius Therapeutics, Inc. Our principal executive office is located at 399 Binney Street, Cambridge, Massachusetts, and our telephone number is (617) 679-9600. Our website address is *www.rubiustx.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.

On July 20, 2018, we completed our initial public offering, or IPO, pursuant to which we issued and sold 12,055,450 shares of common stock, inclusive of 1,572,450 shares pursuant to the full exercise of the underwriters' option to purchase additional shares. We received proceeds of $254.3 million after deducting underwriting discounts and commissions and other offering costs.

We are an "emerging growth company" as defined in the Jumpstart Our Business Startups Act of 2012. We will remain an emerging growth company until the earlier of: (i) the last day of the fiscal year (a) following the fifth anniversary of the completion of the IPO, (b) in which we have total annual gross revenue of at least $1.07 billion, or (c) in which we are deemed to be a large accelerated filer, which means the market value of our common stock that is held by non-affiliates exceeds $700.0 million as of the prior June 30th, and (ii) the date on which we have issued more than $1.0 billion in non-convertible debt during the prior three-year period.

Financial Information and Segments

The financial information required under this Item 1 is incorporated herein by reference to the section of this Annual Report titled "Part II—Item 8—Financial Statements and Supplementary Data. The company manages its operations as a single segment for the purposes of assessing performance and making operating decisions. The company is developing red cell therapeutics for the treatment of patients with severe diseases. All of the company's tangible assets are held in the United States. See Note 2 to our consolidated audited financial statements included in this Annual Report on Form 10-K. For financial information regarding our business, see "Part II—Item 7—Management's Discussion and Analysis of Financial Condition and Results of Operations" of this Annual Report on Form 10-K and our consolidated audited financial statements and related notes included elsewhere in this Annual Report on Form 10-K.

Available Information

Our Internet address is *www.rubiustx.com*. Our Annual Reports on Form 10-K, Quarterly Reports on Form 10-Q, Current Reports on Form 8-K, including exhibits, proxy and information statements and amendments to those reports filed or furnished pursuant to Sections 13(a), 14, and 15(d) of the Securities Exchange Act of 1934, as amended, or the Exchange Act, are available through the "Investors and Media" portion of our website free of charge as soon as reasonably practicable after we electronically file such material with, or furnish it to, the SEC. Information on our website is not part of this Annual Report on Form 10-K or any of our other securities filings unless specifically incorporated herein by reference. Our filings with the SEC may be accessed through the SEC's Interactive Data Electronic Applications system at *http://www.sec.gov*. All statements made in any of our securities filings, including all forward-looking statements or information, are made as of the date of the document in which the statement is included, and we do not assume or undertake any obligation to update any of those statements or documents unless we are required to do so by law.

Item 1A. Risk Factors

Our business is subject to numerous risks. You should carefully consider the risks described below, as well as the other information in this Annual Report on Form 10-K, including our consolidated financial statements and the related notes and "Management's discussion and analysis of financial condition and results of operations," and in our other filings with the Securities and Exchange Commission. The occurrence of any of the events or developments described below could harm our business, financial condition, results of operations and growth prospects. In such an event, the market price of our common stock could decline and you may lose all or part of your investment. Additional risks and uncertainties not presently known to us or that we currently deem immaterial also may impair our business operations.

Risks related to our business, technology and industry

We have incurred net losses in every year since our inception and anticipate that we will continue to incur net losses in the future.

We are a preclinical-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 in clinical development or approved for commercial sale and have not generated any revenue from product sales to date, and we 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 2013. For the years ended December 31, 2018, 2017 and 2016, we reported net losses of $89.2 million, $43.8 million and $11.0 million, respectively. As December 31, 2018, we had an accumulated deficit of $150.1 million. 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, our product candidates. We anticipate that our expenses will increase substantially if, and as, we:

- conduct clinical trials for our product candidates;
- further develop our RED PLATFORM;
- continue to discover and develop additional product candidates;
- maintain, expand and protect our intellectual property portfolio;
- hire additional clinical, scientific manufacturing and commercial personnel;
- expand in-house manufacturing capabilities, including through the renovation, customization and operation of our recently purchased manufacturing facility;
- establish a commercial manufacturing source and secure supply chain capacity sufficient to provide commercial quantities of any product candidates for which we may obtain regulatory approval;
- acquire or in-license other product candidates and technologies;
- seek regulatory approvals for any product candidates that successfully complete clinical trials;
- establish a sales, marketing and distribution infrastructure to commercialize any products for which we may obtain regulatory approval; and

- add operational, regulatory, financial and management information systems and personnel, including personnel to support our product development and planned future commercialization efforts, as well as any additional infrastructure necessary to function as a public company.

To become and remain profitable, we or any potential future collaborator must develop and eventually commercialize products with significant market potential at an adequate profit margin after cost of goods sold and other expenses. This will require us to be successful in a range of challenging activities, including completing preclinical studies and clinical trials, obtaining marketing approval for product candidates, obtaining adequate reimbursement for product candidates, manufacturing, marketing and selling products for which we may obtain marketing approval and satisfying any post-marketing requirements. We may never succeed in any or all of these activities and, even if we do, we may never generate revenue that is significant or large enough to achieve profitability. If we do achieve profitability, we may not be able to sustain or increase profitability on a quarterly or annual basis. Our failure to become and remain profitable would decrease the value of our company and could impair our ability to raise capital, maintain our research and development efforts, expand our business or continue our operations. A decline in the value of our company also could cause our stockholders to lose all or part of their investment.

Even if we succeed in commercializing one or more of our product candidates, we will continue to incur substantial research and development and other expenditures to develop and market additional product candidates. We may encounter unforeseen expenses, difficulties, complications, delays and other unknown factors that may adversely affect our business. The size of our future net losses will depend, in part, on the rate of future growth of our expenses and our ability to generate revenue. Our prior losses and expected future losses have had and will continue to have an adverse effect on our stockholders' equity and working capital.

We will require additional capital to fund our operations and if we fail to obtain necessary financing, we will not be able to complete the development and commercialization of our product candidates.

Our operations have consumed substantial amounts of cash since inception. We expect to continue to spend substantial amounts to conduct further research and development and preclinical or nonclinical testing and studies and clinical trials of our current and future programs, to build a supply chain, to seek regulatory approvals for our product candidates and to launch and commercialize any products for which we receive regulatory approval, including potentially building our own commercial organization. As of December 31, 2018, we had $404.1 million of cash, cash equivalents and investments. Based on our current operating plan, we believe that our existing cash, cash equivalents and investments, will enable us to fund our operating expenses, capital expenditure requirements, including the ongoing renovation and customization of the manufacturing facility we purchased in July 2018, and debt service payments into 2021. However, our future capital requirements and the period for which our existing resources will support our operations may vary significantly from what we expect, and we will in any event require additional capital in order to complete clinical development of any of our current programs. Our monthly spending levels will vary based on new and ongoing development and corporate activities. Because the length of time and activities associated with development of our product candidates is highly uncertain, we are unable to estimate the actual funds we will require for development and any approved marketing and commercialization activities. Our future funding requirements, both near and long-term, will depend on many factors, including, but not limited to:

- the initiation, progress, timing, costs and results of preclinical or nonclinical testing and studies and clinical trials for our product candidates;
- the clinical development plans we establish for our product candidates;
- the number and characteristics of product candidates that we develop or may in-license;
- the terms of any collaboration agreements we may choose to conclude;
- the outcome, timing and cost of meeting regulatory requirements established by the U.S. Food and Drug Administration, or FDA, the European Medicines Agency, or EMA, and other comparable foreign regulatory authorities;

- the cost of filing, prosecuting, defending and enforcing our patent claims and other intellectual property rights;
- the cost of defending intellectual property disputes, including patent infringement actions brought by third parties against us or our product candidates;
- the effect of competing technological and market developments;
- the costs of establishing and maintaining a supply chain for the development and manufacture of our product candidates;
- the cost and timing of establishing, expanding and scaling manufacturing capabilities; and
- the cost of establishing sales, marketing and distribution capabilities for any product candidates for which we may receive regulatory approval in regions where we choose to commercialize our products on our own.

We do not have any committed external source of funds or other support for our development efforts and we cannot be certain that additional funding will be available on acceptable terms, or at all. Until we can generate sufficient product or royalty revenue to finance our cash requirements, which we may never do, we expect to finance our future cash needs through a combination of public or private equity offerings, debt financings, collaborations, strategic alliances, licensing arrangements and other marketing or distribution arrangements. If we raise additional funds through public or private equity offerings, the terms of these securities may include liquidation or other preferences that adversely affect our stockholders' rights. Further, to the extent that we raise additional capital through the sale of common stock or securities convertible into or exchangeable for common stock, our stockholders' ownership interest will be diluted. If we raise additional capital through debt financing, we would be subject to fixed payment obligations and 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 we raise additional capital through marketing and distribution arrangements or other collaborations, strategic alliances or licensing arrangements with third parties, we may have to relinquish certain valuable rights to our product candidates, technologies, future revenue streams or research programs or grant licenses on terms that may not be favorable to us. We also could be required to seek collaborators for one or more of our current or future product candidates at an earlier stage than otherwise would be desirable or relinquish our rights to product candidates or technologies that we otherwise would seek to develop or commercialize ourselves. 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 one or more of our products or product candidates or one or more of our other research and development initiatives. Any of the above events could significantly harm our business, prospects, financial condition and results of operations and cause the price of our common stock to decline.

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

We may seek additional capital through a combination of public and private equity offerings, debt financings, strategic partnerships and alliances and licensing arrangements. To the extent that we raise additional capital through the sale of equity or convertible debt securities, our stockholders' ownership interest will be diluted and the terms may include liquidation or other preferences that adversely affect their rights as a stockholder. The incurrence of indebtedness would result in increased fixed payment obligations and could involve certain restrictive covenants, such as limitations on our ability to incur additional debt, limitations on our ability to acquire or license intellectual property rights and other operating restrictions that could adversely impact our ability to conduct our business. If we raise additional funds through strategic partnerships and alliances and licensing arrangements with third parties, we may have to relinquish valuable rights to our technologies or product candidates or grant licenses on terms unfavorable to us.

We have a limited operating history, which may make it difficult to evaluate our technology and product development capabilities and predict our future performance.

We are early in our development efforts and we have not initiated clinical trials for any of our product candidates. We were formed in 2013, have no products approved for commercial sale and have not generated any revenue from product sales. Our ability to generate product revenue or profits, which we do not expect will occur for many years, if ever, will

depend on the successful development and eventual commercialization of our product candidates, which may never occur. We may never be able to develop or commercialize a marketable product.

All of our programs require additional preclinical research and development, clinical development, regulatory approval in multiple jurisdictions, obtaining manufacturing supply, capacity and expertise, building of a commercial organization, substantial investment and significant marketing efforts before we generate any revenue from product sales. Other programs of ours require additional discovery research and then preclinical development. In addition, our product candidates must be approved for marketing by the FDA or certain other health regulatory agencies, including the EMA, before we may commercialize any product.

Our limited operating history, particularly in light of the rapidly evolving cellular therapeutics field, may make it difficult to evaluate our technology and industry and predict our future performance. Our short history as an operating company makes any assessment of our future success or viability subject to significant uncertainty. We will encounter risks and difficulties frequently experienced by early-stage companies in rapidly evolving fields. If we do not address these risks successfully, our business will suffer. Similarly, we expect that our financial condition and operating results will fluctuate significantly from quarter to quarter and year to year due to a variety of factors, many of which are beyond our control. As a result, our shareholders should not rely upon the results of any quarterly or annual period as an indicator of future operating performance.

In addition, as an early-stage company, we have encountered unforeseen expenses, difficulties, complications, delays and other known and unknown circumstances. As we advance our product candidates, we will need to transition from a company with a research focus to a company capable of supporting clinical development and if successful, commercial activities. We may not be successful in such a transition.

Our business is highly dependent on the success of our initial product candidates targeting rare diseases, cancer and autoimmune diseases. All of our product candidates will require significant additional nonclinical and clinical development before we can seek regulatory approval for and launch a product commercially.

Our business and future success depends on our ability to obtain regulatory approval of and then successfully launch and commercialize our initial product candidates targeting rare diseases, cancer and autoimmune diseases, including RTX-134, RTX-240 (formerly RTX-212) and others that may be selected from preclinical programs. We filed an investigational new drug application, or IND, for RTX-134 in the first quarter of 2019 and plan to file INDs for additional Red Cell Therapeutic, or RCT, product candidates during 2020, 2021 and thereafter. In particular, RTX-134, as our first planned clinical program, may experience preliminary complications surrounding trial execution, such as complexities surrounding regulatory acceptance of our IND, trial design and establishing trial protocols, patient recruitment and enrollment, quality and supply of clinical doses, safety issues, a lack of clinically relevant activity, or shorter than expected circulation time of RTX-134 *in vivo*.

All of our product candidates are in the early stages of development and will require additional nonclinical and clinical development, regulatory review and approval in multiple jurisdictions, substantial investment, access to sufficient commercial manufacturing capacity and significant marketing efforts before we can generate any revenue from product sales. In addition, because RTX-134 is our most advanced product candidate, if RTX-134 encounters safety, efficacy, supply or manufacturing problems, developmental delays, regulatory or commercialization issues or other problems, our development plans and business would be significantly harmed.

The successful development of cellular therapeutics, such as our RCTs, is highly uncertain.

Successful development of cellular therapeutics, such as our RCTs, is highly uncertain and is dependent on numerous factors, many of which are beyond our control. Cellular therapeutics that appear promising in the early phases of development may fail to reach the market for several reasons, including:

- nonclinical or preclinical testing or study results may show our RCTs to be less effective than desired or to have harmful or problematic side effects or toxicities;

- clinical trial results may show our RCTs to be less effective than expected (e.g., a clinical trial could fail to meet its primary endpoint(s)) or to have unacceptable side effects or toxicities;

- clinical trial results may show that the relatively long circulating time of our RCTs, expected to be up to approximately 120 days, compared to other therapeutics may have unacceptable side effects, toxicities or other negative consequences;

- failure to receive the necessary regulatory approvals or a delay in receiving such approvals. Among other things, such delays may be caused by slow enrollment in clinical trials, patients dropping out of trials, length of time to achieve trial endpoints, additional time requirements for data analysis, or biologics license application, or BLA, preparation, discussions with the FDA, an FDA request for additional nonclinical or clinical data, or unexpected safety or manufacturing issues;

- manufacturing costs, formulation issues, pricing or reimbursement issues, or other factors that make our RCT therapies uneconomical; and

- proprietary rights of others and their competing products and technologies that may prevent our RCT therapies from being commercialized.

The length of time necessary to complete clinical trials and to submit an application for marketing approval for a final decision by a regulatory authority may be difficult to predict for cellular therapies, in large part because of the limited regulatory history.

Even if we are successful in obtaining market approval, commercial success of any approved products will also depend in large part on the availability of insurance coverage and adequate reimbursement from third-party payors, including government payors, such as the Medicare and Medicaid programs, and managed care organizations, which may be affected by existing and future healthcare reform measures designed to reduce the cost of healthcare. Third-party payors may limit the definition of the target treatment population to one smaller than that implied in the label granted by regulatory authorities, and could require us to conduct additional studies, including post-marketing studies related to the cost-effectiveness of a product, to qualify for reimbursement, which could be costly and divert our resources. If government and other healthcare payors were not to provide adequate insurance coverage and reimbursement levels for one any of our products once approved, market acceptance and commercial success would be reduced.

In addition, if any of our products are approved for marketing, we will be subject to significant regulatory obligations regarding the submission of safety and other post-marketing information and reports and registration, and will need to continue to comply (or ensure that our third-party providers comply) with current good manufacturing practices, or cGMPs, and good clinical practices, or GCPs, for any clinical trials that we conduct post-approval. In addition, there is always the risk that we or a regulatory authority might identify previously unknown problems with a product post-approval, such as adverse events of unanticipated severity or frequency. Compliance with these requirements is costly and any failure to comply or other issues with our product candidates' post-approval could have a material adverse effect on our business, financial condition and results of operations.

Our RCT product candidates are based on a new technology, which makes it difficult to predict the time and cost of development and of subsequently obtaining regulatory approval, if at all.

Our RCT technology is relatively new and no products based on genetically engineered red cells have been approved to date in the United States or the European Union. As such it is difficult to accurately predict the developmental challenges we may incur for our product candidates as they proceed through product discovery or identification, preclinical studies and clinical trials. In addition, because we have not commenced clinical trials, we have not yet been able to assess safety in humans, and there may be short-term or long-term effects from treatment with any product candidates that we develop that we cannot predict at this time. Also, animal models may not exist for some of the diseases we choose to pursue in our programs. Furthermore, cellular therapies, such as our RCT product candidates, have a limited circulating time in animals as they are recognized as foreign by the host animal and therefore cleared by the complement-mediated reticuloendothelial system, which limits the safety and toxicology assessments that we can

conduct in preclinical species. As a result of these factors, it is more difficult for us to predict the time and cost of product candidate development, and we cannot predict whether the application of our RED PLATFORM, or any similar or competitive cellular technologies, will result in the identification, development, and regulatory approval of any products. There can be no assurance that any development problems we experience in the future related to our RED PLATFORM or any of our research programs will not cause significant delays or unanticipated costs, or that such development problems can be solved. Any of these factors may prevent us from completing our preclinical studies or any clinical trials that we may initiate or commercializing any product candidates we may develop on a timely or profitable basis, if at all.

The clinical trial requirements of the FDA, the EMA and other regulatory authorities and the criteria these regulators use to determine the safety and efficacy of a product candidate vary substantially according to the type, complexity, novelty and intended use and market of the product candidate. No products based on genetically engineered red cells have been approved to date by regulators. As a result, the regulatory approval process for product candidates such as ours is uncertain and may be more expensive and take longer than the approval process for product candidates based on other, better known or more extensively studied technologies. It is difficult to determine how long it will take or how much it will cost to obtain regulatory approvals for our product candidates in either the United States or the European Union or other regions of the world or how long it will take to commercialize our product candidates. Delay or failure to obtain, or unexpected costs in obtaining, the regulatory approval necessary to bring a potential product candidate to market could decrease our ability to generate sufficient product revenue, and our business, financial condition, results of operations and prospects may be harmed.

The FDA, the EMA and other regulatory authorities may implement additional regulations or restrictions on the development and commercialization of our product candidates, which may be difficult to predict.

The FDA, the EMA and regulatory authorities in other countries have each expressed interest in further regulating biotechnology products, such as cellular therapies. Agencies at both the federal and state level in the United States, as well as the U.S. Congressional committees and other governments or governing agencies, have also expressed interest in further regulating the biotechnology industry. Such action may delay or prevent commercialization of some or all of our product candidates. Adverse developments in clinical trials of cellular therapy products conducted by others may cause the FDA or other oversight bodies to change the requirements for approval of any of our product candidates. Similarly, the EMA governs the development of cellular therapies in the European Union and may issue new guidelines concerning the development and marketing authorization for cellular therapy products and require that we comply with these new guidelines. These regulatory review agencies and committees and the new requirements or guidelines they promulgate may lengthen the regulatory review process, require us to perform additional studies or trials, increase our development costs, lead to changes in regulatory positions and interpretations, delay or prevent approval and commercialization of our product candidates or lead to significant post-approval limitations or restrictions. As we advance our product candidates, we will be required to consult with these regulatory agencies and comply with applicable requirements and guidelines. If we fail to do so, we may be required to delay or discontinue development of such product candidates. These additional processes may result in a review and approval process that is longer than we otherwise would have expected. Delays as a result of an increased or lengthier regulatory approval process or further restrictions on the development of our product candidates can be costly and could negatively impact our ability to complete clinical trials and commercialize our current and future product candidates in a timely manner, if at all.

Clinical development involves a lengthy and expensive process, with an uncertain outcome. We may incur additional costs or experience delays in completing, or ultimately be unable to complete, the development and commercialization of any product candidates.

To obtain the requisite regulatory approvals to commercialize any product candidates, we must demonstrate through extensive preclinical studies and clinical trials that our products are safe and effective in humans. Clinical testing is expensive, difficult to design and implement and can take many years to complete, and its outcome is inherently uncertain. We may be unable to establish clinical endpoints that applicable regulatory authorities would consider clinically meaningful, and a clinical trial can fail at any stage of testing. The outcome of nonclinical studies and early clinical trials may not be predictive of the success of later clinical trials, and interim results of a clinical trial do not necessarily predict final results. Differences in trial design between early-stage clinical trials and later-stage clinical trials make it difficult to extrapolate the results of earlier clinical trials to later clinical trials. Moreover, nonclinical and

clinical data are often susceptible to varying interpretations and analyses, and many companies that have believed their product candidates performed satisfactorily in nonclinical studies and clinical trials have nonetheless failed to obtain marketing approval of their products.

Successful completion of clinical trials is a prerequisite to submitting a BLA to the FDA, a Marketing Authorization Application, or MAA, to the EMA, and similar marketing applications to comparable foreign regulatory authorities, for each product candidate and, consequently, the ultimate approval and commercial marketing of any product candidates. We do not know whether any of our clinical trials will begin or be completed on schedule, if at all.

We may experience delays in completing our preclinical or nonclinical testing and studies and initiating or completing clinical trials. We also may experience numerous unforeseen events during, or as a result of, any future clinical trials that we could conduct that could delay or prevent our ability to receive marketing approval or commercialize our product candidates, including:

- we may be unable to generate sufficient preclinical, toxicology, or other *in vivo* or *in vitro* data to support the initiation of clinical trials;
- regulators or institutional review boards, or IRBs, or ethics committees may not authorize us or our investigators to commence a clinical trial or conduct a clinical trial at a prospective trial site;
- we may experience delays in reaching, or fail to reach, agreement on acceptable terms with prospective trial sites and prospective contract research organizations, or CROs, the terms of which can be subject to extensive negotiation and may vary significantly among different CROs and trial sites;
- clinical trials of any product candidates may fail to show safety, purity or potency, or produce negative or inconclusive results and we may decide, or regulators may require us, to conduct additional nonclinical studies or clinical trials or we may decide to abandon product development programs;
- the number of patients required for clinical trials of any product candidates may be larger than we anticipate, enrollment in these clinical trials may be slower than we anticipate or participants may drop out of these clinical trials or fail to return for post-treatment follow-up at a higher rate than we anticipate;
- we may need to add new or additional clinical trial sites;
- our third-party contractors may fail to comply with regulatory requirements or meet their contractual obligations to us in a timely manner, or at all, or may deviate from the clinical trial protocol or drop out of the trial, which may require that we add new clinical trial sites or investigators;
- the cost of preclinical or nonclinical testing and studies and clinical trials of any product candidates may be greater than we anticipate or greater than our available financial resources;
- the supply or quality of our product candidates or other materials necessary to conduct clinical trials of our product candidates may be insufficient or inadequate;
- RCTs may circulate longer or shorter in humans than anticipated;
- our product candidates may have undesirable side effects or other unexpected characteristics, causing us or our investigators, regulators or IRBs or ethics committees to suspend or terminate the trials, or reports may arise from preclinical or clinical testing of other therapies for rare diseases, cancer and autoimmune diseases or additional diseases that we target that raise safety or efficacy concerns about our product candidates;
- clinical trials of our product candidates may produce negative or inconclusive results, which may result in our deciding, or regulators requiring us, to conduct additional clinical trials or abandon product development programs; and
- the FDA or other regulatory authorities may require us to submit additional data such as long-term toxicology studies or impose other requirements before permitting us to initiate a clinical trial.

We could also encounter delays if a clinical trial is suspended or terminated by us, the IRBs of the institutions in which such trials are being conducted, or the FDA or other regulatory authorities, or recommended for suspension or termination by the Data Safety Monitoring Board, or DSMB, for such trial. A suspension or termination may be imposed 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 product or treatment, failure to establish or achieve clinically meaningful trial endpoints, changes in governmental regulations or administrative actions or lack of adequate funding to continue the clinical trial. Many of the factors that cause, or lead to, a delay in the commencement or completion of clinical trials may also ultimately lead to the denial of regulatory approval of our product candidates. Further, the FDA or other regulatory authorities may disagree with our clinical trial design and our interpretation of data from clinical trials, or may change the requirements for approval even after they have reviewed and commented on the design for our clinical trials.

Our product development costs will increase if we experience delays in clinical testing or marketing approvals. We do not know whether any of our preclinical or nonclinical testing and studies or clinical trials will begin as planned, will need to be restructured or will be completed on schedule, or at all. Significant preclinical or nonclinical testing and studies or clinical trial delays also could shorten any periods during which we may have the exclusive right to commercialize our product candidates and may allow our competitors to bring products to market before we do, potentially impairing our ability to successfully commercialize our product candidates and harming our business and results of operations. Any delays in our nonclinical or future clinical development programs may harm our business, financial condition and prospects significantly.

Preclinical development is uncertain. Our preclinical programs may experience delays or may never advance to clinical trials, which would adversely affect our ability to obtain regulatory approvals or commercialize these programs on a timely basis or at all, which would have an adverse effect on our business.

All of our product candidates are still in the preclinical stage, and their risk of failure is high. Before we can commence clinical trials for a product candidate, we must complete extensive preclinical testing and studies that support our planned INDs in the United States, or similar applications in other jurisdictions. We cannot be certain of the timely completion or outcome of our preclinical testing and studies and cannot predict if the FDA or other regulatory authorities will accept our proposed clinical programs or if the outcome of our preclinical testing and studies will ultimately support the further development of our programs. As a result, we cannot be sure that we will be able to submit INDs or similar applications for our preclinical programs on the timelines we expect, if at all, and we cannot be sure that submission of INDs or similar applications will result in the FDA or other regulatory authorities allowing clinical trials to begin.

Our planned clinical trials or those of our future collaborators may reveal significant adverse events not seen in our preclinical or nonclinical studies and may result in a safety profile that could inhibit regulatory approval or market acceptance of any of our product candidates.

Before obtaining regulatory approvals for the commercial sale of any products, we must demonstrate through lengthy, complex and expensive preclinical studies and clinical trials that our product candidates are both safe and effective for use in each target indication. Clinical testing is expensive and can take many years to complete, and its outcome is inherently uncertain. Failure can occur at any time during the clinical trial process. The results of preclinical studies and early clinical trials of our product candidates may not be predictive of the results of later-stage clinical trials. In addition, initial success in clinical trials may not be indicative of results obtained when such trials are completed. There is typically an extremely high rate of attrition from the failure of product candidates proceeding through clinical trials. Our RCTs are produced from O negative donor blood stem cells and we believe can therefore be used as allogeneic therapies in approximately 95% of patients. However, following repeated dosing some patients may develop antibodies to blood antigens on our RCTs. These antibodies could reduce the efficacy of our RCTs or result in undesirable side effects. Product candidates in later stages of clinical trials also may fail to show the desired safety and efficacy profile despite having progressed through nonclinical studies and initial clinical trials. A number of companies in the biopharmaceutical industry have suffered significant setbacks in advanced clinical trials due to lack of efficacy or unacceptable safety issues, notwithstanding promising results in earlier trials. Most product candidates that commence clinical trials are

never approved as products and there can be no assurance that any of our current or future clinical trials will ultimately be successful or support further clinical development of any of our product candidates.

We intend to develop RTX-240 and RTX-224, and may develop future product candidates, alone and in combination with one or more cancer therapies. The uncertainty resulting from the use of our product candidates in combination with other cancer therapies may make it difficult to accurately predict side effects in future clinical trials.

If significant adverse events or other side effects are observed in any of our current or future clinical trials, we may have difficulty recruiting patients to our clinical trials, patients may drop out of our trials, or we may be required to abandon the trials or our development efforts of one or more product candidates altogether. Although our RCTs are designed to be enucleated, a small percentage may retain a nucleus, which could result in unexpected or undesirable side effects. We, the FDA or other applicable regulatory authorities, or an IRB may suspend clinical trials of a product candidate at any time for various reasons, including a belief that subjects in such trials are being exposed to unacceptable health risks or adverse side effects. Some potential therapeutics developed in the biotechnology industry that initially showed therapeutic promise in early-stage trials have later been found to cause side effects that prevented their further development. Even if the side effects do not preclude the drug from obtaining or maintaining marketing approval, undesirable side effects may inhibit market acceptance of the approved product due to its tolerability versus other therapies. Any of these developments could materially harm our business, financial condition and prospects.

Positive results from early preclinical studies of our product candidates are not necessarily predictive of the results of later preclinical studies and any future clinical trials of our product candidates. If we cannot replicate the positive results from our earlier preclinical studies of our product candidates in our later preclinical studies and future clinical trials, we may be unable to successfully develop, obtain regulatory for and commercialize our product candidates.

Any positive results from our preclinical studies of our product candidates may not necessarily be predictive of the results from required later preclinical studies and clinical trials. Similarly, even if we are able to complete our planned preclinical studies or any future clinical trials of our product candidates according to our current development timeline, the positive results from such preclinical studies and clinical trials of our product candidates may not be replicated in subsequent preclinical studies or clinical trial results.

Many companies in the pharmaceutical and biotechnology industries have suffered significant setbacks in late-stage clinical trials after achieving positive results in early-stage development and we cannot be certain that we will not face similar setbacks. These setbacks have been caused by, among other things, preclinical and other nonclinical findings made while clinical trials were underway, or safety or efficacy observations made in preclinical studies and clinical trials, including previously unreported adverse events. Moreover, preclinical, nonclinical and clinical data are often susceptible to varying interpretations and analyses and many companies that believed their product candidates performed satisfactorily in preclinical studies and clinical trials nonetheless failed to obtain FDA or EMA approval.

If we encounter difficulties enrolling patients in our 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. The enrollment of patients depends on many factors, including:

- the severity of the disease under investigation;
- the patient eligibility and exclusion 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 trial sites;

- the design of the trial;
- our ability to recruit clinical trial investigators with the appropriate competencies and experience;
- 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 in clinical development or approved for the indications we are investigating;
- the efforts to facilitate timely enrollment in clinical trials;
- the patient referral practices of physicians;
- the ability to monitor patients adequately during and after treatment;
- 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.

Genetically defined diseases generally, and especially those for which our current rare disease product candidates are targeted, have low incidence and prevalence. For example, the prevalence of phenylketonuria, or PKU, is estimated to be 1 in 10,000 to 1 in 15,000 newborns in the United States and Europe and varies considerably in populations elsewhere around the world. This could pose obstacles to the timely recruitment and enrollment of a sufficient number of eligible patients into our proposed clinical and the other risks described above.

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. Moreover, because our product candidates represent a departure from more commonly used methods for our targeted therapeutic areas, potential patients and their doctors may be inclined to use conventional or newly launched competitive therapies, rather than enroll patients in any future clinical trial.

Delays in patient enrollment may result in increased costs or may affect the timing or outcome of the planned clinical trials, which could prevent completion of these trials and adversely affect our ability to advance the development of our product candidates.

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

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

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

We are subject to numerous environmental, health and safety laws and regulations, including those governing laboratory procedures and the handling, use, storage, treatment and disposal of hazardous materials and wastes. Our research and development activities involve the use of biological and hazardous materials and produce hazardous waste products. We generally contract with third parties for the disposal of these materials and wastes. We cannot eliminate the risk of contamination or injury from these materials, which could cause an interruption of our commercialization efforts, research and development efforts and business operations, environmental damage resulting in costly clean-up and liabilities under applicable laws and regulations governing the use, storage, handling and disposal of these materials and specified waste products. Although we believe that the safety procedures utilized by our third-party manufacturers for handling and disposing of these materials generally comply with the standards prescribed by these laws and regulations, we cannot guarantee that this is the case or eliminate the risk of accidental contamination or injury from these materials. In such an event, we may be held liable for any resulting damages and such liability could exceed our resources and state or federal or other applicable authorities may curtail our use of certain materials and/or interrupt our business operations. Furthermore, environmental laws and regulations are complex, change frequently and have tended to become more stringent. We cannot predict the impact of such changes and cannot be certain of our future compliance. In addition, we may incur substantial costs in order to comply with current or future environmental, health and safety laws and regulations. These current or future laws and regulations may impair our research, development or production efforts. Failure to comply with these laws and regulations also may result in substantial fines, penalties or other sanctions.

Although we maintain workers' compensation insurance to cover us for costs and expenses we may incur due to injuries to our employees resulting from the use of hazardous materials or other work-related injuries, this insurance may not provide adequate coverage against potential liabilities. We do not carry specific biological waste or hazardous waste insurance coverage, workers compensation or property and casualty and general liability insurance policies that include coverage for damages and fines arising from biological or hazardous waste exposure or contamination.

If product liability lawsuits are brought against us, we may incur substantial liabilities and may be required to limit commercialization of our product candidates.

We face an inherent risk of product liability as a result of testing our product candidates in clinical trials and will face an even greater risk if we commercialize any products. For example, we may be sued if our product candidates cause or are perceived to cause injury or are found to be otherwise unsuitable during clinical trials, manufacturing, marketing or sale. Any such product liability claims may include allegations of defects in manufacturing, defects in design, a failure to warn of dangers inherent in the product, negligence, strict liability or a breach of warranties. Claims could also be asserted under state consumer protection acts. If we cannot successfully defend ourselves against product liability claims, we may incur substantial liabilities or be required to limit commercialization of our product candidates. Even successful defense would require significant financial and management resources. Regardless of the merits or eventual outcome, liability claims may result in:

- inability to bring a product candidate to the market;
- decreased demand for our products;
- injury to our reputation;
- withdrawal of clinical trial participants and inability to continue clinical trials;
- initiation of investigations by regulators;
- costs to defend the related litigation;
- diversion of management's time and our resources;

- substantial monetary awards to trial participants or patients;
- product recalls, withdrawals or labeling, marketing or promotional restrictions;
- loss of revenue;
- exhaustion of any available insurance and our capital resources;
- the inability to commercialize any product candidate; and
- declines in our share price.

Since we have not yet commenced clinical trials, we do not yet hold clinical trial or product liability insurance. Our inability to obtain sufficient product liability insurance at an acceptable cost to protect against potential product liability claims could prevent or inhibit the commercialization of products we develop, alone or with collaborators. If and when coverage is secured, our insurance policies may also have various exclusions, and we may be subject to a product liability claim for which we have no coverage. We may have to pay any amounts awarded by a court or negotiated in a settlement that exceed our coverage limitations or that are not covered by our insurance, and we may not have, or be able to obtain, sufficient capital to pay such amounts. Even if our agreements with any future corporate collaborators entitle us to indemnification against losses, such indemnification may not be available or adequate should any claim arise.

The market opportunities for our product candidates may be limited to those patients who are ineligible for or have failed prior treatments and may be small, and our estimates of the prevalence of our target patient populations may be inaccurate.

Cancer and autoimmune therapies are sometimes characterized as first-line, second-line, third-line and even fourth-line, and the FDA often approves new therapies initially only for last-line use. Initial approvals for new cancer and autoimmune therapies are often restricted to later lines of therapy, and in the case of cancer specifically, for patients with advanced or metastatic disease. This will limit the number of patients who may be eligible for such new therapies, which may include our product candidates.

Our projections of both the number of people who have the diseases we are targeting, as well as the subset of people with these diseases in a position to receive our therapies, if approved, are based on our beliefs and estimates. These estimates have been derived from a variety of sources, including scientific literature, input from key opinion leaders, patient foundations, or secondary market research databases, and may prove to be incorrect. Further, new studies may change the estimated incidence or prevalence of these diseases. The number of patients may turn out to be lower than expected. Additionally, the potentially addressable patient population for our product candidates may be limited or may not be amenable to treatment with our product candidates. For instance, we expect our product candidates targeting rare diseases to target the smaller patient populations that suffer from the respective diseases we seek to treat. Furthermore, regulators and payors may further narrow the therapy-accessible treatment population. Even if we obtain significant market share for our product candidates, because certain of the potential target populations are small, we may never achieve profitability without obtaining regulatory approval for additional indications.

We expect to develop RTX-240 and RTX-224, and potentially future product candidates, alone and in combination with other therapies, and safety or supply issues with combination-use products may delay or prevent development and approval of our product candidates.

We intend to develop RTX-240 and RTX-224, and likely other product candidates, alone and in combination with one or more cancer therapies, both approved and unapproved. Even if any product candidate we develop were to receive marketing approval or be commercialized for use in combination with other existing therapies, we would continue to be subject to the risks that the FDA or similar regulatory authorities outside of the United States could revoke approval of the therapy used in combination with our product candidate or that safety, efficacy, manufacturing or supply issues could arise with these existing therapies. Combination therapies are commonly used for the treatment of cancer, and we would be subject to similar risks if we develop any of our product candidates for use in combination with other drugs or for

indications other than cancer. Similarly, if the therapies we use in combination with our product candidates are replaced as the standard of care for the indications we choose for any of our product candidates, the FDA or similar regulatory authorities outside of the United States may require us to conduct additional clinical trials. The occurrence of any of these risks could result in our own products, if approved, being removed from the market or being less successful commercially.

We may also evaluate RTX-240 and RTX-224 or any other future product candidates in combination with one or more cancer therapies that have not yet been approved for marketing by the FDA or similar regulatory authorities outside of the United States. We will not be able to market and sell RTX-240, RTX-224 or any product candidate we develop in combination with any such unapproved cancer therapies that do not ultimately obtain marketing approval. The regulations prohibiting the promotion of products for unapproved uses are complex and subject to substantial interpretation by the FDA and other government agencies. In addition, there are additional risks similar to the ones described for our products currently in development and clinical trials that result from the fact that such cancer therapies are unapproved, such as the potential for serious adverse effects, delay in their clinical trials and lack of FDA approval.

If the FDA or similar regulatory authorities outside of the United States do not approve these other drugs or revoke their approval of, or if safety, efficacy, manufacturing, or supply issues arise with, the drugs we choose to evaluate in combination with RTX-240, RTX-224 or any product candidate we develop, we may be unable to obtain approval of or market RTX-240, RTX-224 or any product candidate we develop.

Cellular therapies are a novel approach and negative perception of any product candidates that we develop could adversely affect our ability to conduct our business or obtain regulatory approvals for such product candidates.

Cellular therapies in general, and RCTs in particular, remain novel and unproven therapies, with no genetically engineered red cell therapy approved to date in the United States or the European Union. RCTs may not gain the acceptance of the public or the medical community. For example, CAR-Ts and other cellular therapies have in some cases caused severe side effects and even mortality and their broader use may therefore be limited. Although our RCTs are fundamentally different than these earlier cellular therapies, they may be viewed in the same vein, limiting their market acceptance. Further, with respect to our RTX-240 and RTX-224 programs, the use of potent T cell and NK cell stimulation as a potential treatment for solid or hematological cancers is a recent scientific development and may not become broadly accepted by physicians, patients, hospitals, cancer treatment centers and others in the medical community.

Our success will depend upon physicians who specialize in the treatment of diseases targeted by our product candidates prescribing treatments that involve the use of our product candidates in lieu of, or in addition to, existing treatments with which they are more familiar and for which greater clinical data may be available. Adverse events in clinical trials of our product candidates or in clinical trials of others developing similar products and the resulting publicity, as well as any other adverse events in the field of cellular therapies, could result in a decrease in demand for any product that we may develop. In addition, responses by the U.S., state or foreign governments to negative public perception or ethical concerns may result in new legislation or regulations that could limit our ability to develop or commercialize any product candidates, obtain or maintain regulatory approval or otherwise achieve profitability. More restrictive statutory regimes, government regulations or negative public opinion would have an adverse effect on our business, financial condition, results of operations and prospects and may delay or impair the development and commercialization of our product candidates or demand for any products we may develop.

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

The biopharmaceutical industry is characterized by intense competition and rapid innovation. Our competitors may be able to develop other compounds, drugs, cellular or gene therapies that are able to achieve similar or better results. Our potential competitors include major multinational pharmaceutical companies, established biotechnology companies, specialty pharmaceutical companies and universities and other research institutions. Many of our competitors have substantially greater financial, technical and other resources, such as larger research and development staff, experienced marketing and manufacturing organizations and well-established sales forces. Smaller or early-stage companies may also

prove to be significant competitors, particularly through collaborative arrangements with large, established companies. Established pharmaceutical companies may also invest heavily to accelerate discovery and development of novel therapeutics or to in-license novel therapeutics that could make the product candidates that we develop obsolete. Mergers and acquisitions in the biotechnology and pharmaceutical industries may result in even more resources being concentrated in our competitors. Competition may increase further as a result of advances in the commercial applicability of technologies and greater availability of capital for investment in these industries. Our competitors, either alone or with collaborative partners, may succeed in developing, acquiring or licensing on an exclusive basis drug, biologic, cellular or gene therapy products that are more effective, safer, more easily commercialized or less costly than our product candidates or may develop proprietary technologies or secure patent protection that we may need for the development of our technologies and products. We believe the key competitive factors that will affect the development and commercial success of our product candidates are efficacy, safety, tolerability, reliability, convenience of use, price and reimbursement.

We anticipate competing with the largest biopharmaceutical companies in the world, such as Novartis AG, Gilead Sciences, Inc., Amgen, Inc., F. Hoffman-La Roche AG (Roche), Johnson & Johnson, GlaxoSmithKline plc, Sanofi S.A., and Pfizer Inc., which are all currently conducting research in cellular therapies, either alone or in partnerships with other parties, and all of which have greater financial and human resources than we currently have. In addition to these fully integrated biopharmaceutical companies, we also compete with those companies whose products target the same indications as our product candidates. Many third parties compete with us in developing various approaches to rare diseases, cancer and autoimmune therapies. They include pharmaceutical companies, biotechnology companies, academic institutions and other research organizations. Any treatments developed by our competitors could be superior to our RCT product candidates. It is possible that these competitors will succeed in developing technologies that are more effective than our RCTs or that would render our cancer targeted RCTs obsolete or noncompetitive. We anticipate that we will face increased competition in the future as additional companies enter our market and scientific developments surrounding other rare diseases, cancer and autoimmune therapies continue to accelerate.

In addition, we have identified four companies that are leveraging the red blood cell as a platform. Erytech Pharma SA is using hypotonic enzyme loading to create products for use in cancer, rare disease and immunology. There are three other companies that rely on loading proteins into mature red cells: Orphan Technologies Ltd., which is developing a range of products aimed at rare diseases; EryDel SpA, which is in late-stage development of dexamethasone loaded red blood cells, or RBCs for the treatment of ataxia telangiectasia; and SQZ Biotechnologies Companies, which is pursuing preclinical applications in cancer, enzyme replacement therapy and immune tolerance using a variety of cell-based approaches.

Outside of RBC based competition, there are companies developing engineered enzymes and specializing in rare diseases, such as Codexis, Inc., which has a product candidate in a Phase 1 trial for the treatment of PKU and Aeglea BioTherapeutics, Inc., which has a product candidate in a Phase 1 trial for the treatment of hyperargininemia. There are a number of gene therapy companies, such as BioMarin Pharmaceutical, Inc., which has active gene therapy programs that include a preclinical PKU product candidate, and Homology Medicines, Inc., which recently declared that it is in IND enabling studies with a gene therapy product candidate and expects to initiate a clinical trial in PKU in the first quarter of 2019. In addition, Moderna, Inc. is in early preclinical work with an mRNA approach to addressing PKU and Synlogic, Inc. is one of several companies developing engineered probiotic therapeutics to treat inborn errors of metabolism and has a product candidate in a Phase 1 trial for the treatment of urea cycle disorders, as well as a product candidate in a Phase 1/2 trial for the treatment of PKU. Finally, Agios Pharmaceuticals, Inc. declared that it is in the early discovery stage with a small molecule approach to PKU treatment.

Even if we obtain regulatory approval to market our product candidates, the availability and price of our competitors' products could limit the demand and the price we are able to charge for our product candidates. We may not be able to implement our business plan if the acceptance of our product candidates is inhibited by price competition or the reluctance of physicians to switch from existing methods of treatment to our product candidates, or if physicians switch to other new drug or biologic products or choose to reserve our product candidates for use in limited circumstances.

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

If any product candidate we develop receives marketing approval, whether as a single agent or in combination with other therapies, it may nonetheless fail to gain sufficient market acceptance by physicians, patients, third-party payors, and others in the medical community. For example, other cancer treatments like chemotherapy, radiation therapy and immunotherapy are well established in the medical community, and doctors may continue to rely on these therapies. If the product candidates we develop do not achieve an adequate level of acceptance, we may not generate significant product revenues and we may not become profitable. The degree of market acceptance of any product candidate, if approved for commercial sale, will depend on a number of factors, including:

- efficacy, safety and potential advantages compared to alternative treatments;
- convenience and ease of administration compared to alternative treatments;
- the willingness of the target patient population to try new therapies and of physicians to prescribe these therapies;
- public perception of new therapies, including cellular therapies;
- the strength of marketing and distribution support;
- the ability to offer our products, if approved, for sale at competitive prices;
- the ability to obtain sufficient third-party insurance coverage and adequate reimbursement, including with respect to the use of the approved product as a combination therapy;
- adoption of a companion diagnostic and/or complementary diagnostic; and
- the prevalence and severity of any side effects.

We will need to grow the size of our organization, and we may experience difficulties in managing this growth.

As of Februrary 28, 2019, we had 142 full-time employees. As our research, development, manufacturing and commercialization plans and strategies develop, and as we transition into operating as a public company, we expect to need additional managerial, operational, sales, marketing, financial and other personnel. Future growth would impose significant added responsibilities on members of management, including:

- identifying, recruiting, compensating, integrating, maintaining and motivating additional employees;
- managing our internal research and development efforts effectively, including identification of clinical candidates, scaling our manufacturing process and navigating the clinical and FDA review process for our product candidates; and
- improving our operational, financial and management controls, reporting systems and procedures.

Our future financial performance and our ability to commercialize our product candidates will depend, in part, on our ability to effectively manage any future growth, and our management may also have to divert a disproportionate amount of its attention away from day-to-day activities in order to devote a substantial amount of time to managing these growth activities.

We currently rely, and for the foreseeable future will continue to rely, in substantial part on certain organizations, advisors and consultants to provide certain services, including many aspects of regulatory affairs, clinical management and manufacturing. There can be no assurance that the services of these organizations, advisors and consultants will

continue to be available to us on a timely basis when needed, or that we can find qualified replacements. In addition, if we are unable to effectively manage our outsourced activities or if the quality or accuracy of the services provided by consultants is compromised for any reason, our clinical trials may be extended, delayed or terminated, and we may not be able to obtain regulatory approval of our product candidates or otherwise advance our business. There can be no assurance that we will be able to manage our existing consultants or find other competent outside contractors and consultants on economically reasonable terms, or at all.

If we are not able to effectively expand our organization by hiring new employees and expanding our groups of consultants and contractors, we may not be able to successfully implement the tasks necessary to further develop and commercialize our product candidates and, accordingly, may not achieve our research, development and commercialization goals.

If we lose key management personnel, or if we fail to recruit additional highly skilled personnel, our ability to identify and develop new or next generation product candidates will be impaired, could result in loss of markets or market share and could make us less competitive.

Our ability to compete in the highly competitive biotechnology and pharmaceutical industries depends upon our ability to attract and retain highly qualified managerial, scientific and medical personnel. We are highly dependent on our management, scientific and medical personnel, including David R. Epstein, our Chairman, Pablo J. Cagnoni, our Chief Executive Officer, Torben Straight Nissen, our President, Andrew Oh, our Chief Financial Officer, Chris Carpenter, our Chief Medical Officer and Spencer Fisk, our Senior Vice President of Manufacturing. The loss of the services of any of our executive officers, other key employees, and other scientific and medical advisors, and our inability to find suitable replacements could result in delays in product development and harm our business.

We conduct our operations at our facilities in Cambridge, Massachusetts and Smithfield, Rhode Island. The New England region is headquarters to many other biopharmaceutical companies and many academic and research institutions. Competition for skilled personnel in our market is intense and may limit our ability to hire and retain highly qualified personnel on acceptable terms or at all.

To induce valuable employees to remain at our company, in addition to salary and cash incentives, we have provided restricted stock and stock options that vest over time. The value to employees of stock options that vest over time may be significantly affected by movements in our stock price that are beyond our control, and may at any time be insufficient to counteract more lucrative offers from other companies. Despite our efforts to retain valuable employees, members of our management, scientific and development teams may terminate their employment with us on short notice. Employment of our key employees is at-will, which means that any of our employees could leave our employment at any time, with or without notice. We do not maintain “key man” insurance policies on the lives of these individuals or the lives of any of our other employees. Our success also depends on our ability to continue to attract, retain and motivate highly skilled junior, mid-level and senior managers as well as junior, mid-level and senior scientific and medical personnel.

Business disruptions could seriously harm our future revenue and financial condition and increase our costs and expenses.

Our operations, and those of our CROs, contract manufacturing organizations, or CMOs, and other contractors and consultants, could be subject to earthquakes, power shortages, telecommunications failures, water shortages, floods, hurricanes, typhoons, fires, extreme weather conditions, medical epidemics and other natural or man-made disasters or business interruptions, for which we are predominantly self-insured. The occurrence of any of these business disruptions could seriously harm our operations and financial condition and increase our costs and expenses. We rely on third-party manufacturers to produce and process our product candidates on a patient by patient basis. Our ability to obtain clinical supplies of our product candidates could be disrupted if the operations of these suppliers are affected by a man-made or natural disaster or other business interruption.

Regulators globally are also imposing greater monetary fines for privacy violations. For example, in 2016, the European Union adopted a new regulation governing data practices and privacy called the General Data Protection Regulation, or GDPR, which became effective on May 25, 2018. The GDPR applies to any company that collects and uses personal

data in connection with offering goods or services to individuals in the European Union or the monitoring of their behavior. Non-compliance with the GDPR may result in monetary penalties of up to €20 million or 4% of worldwide revenue, whichever is higher. The GDPR and other changes in laws or regulations associated with the enhanced protection of certain types of personal data, such as healthcare data or other sensitive information, could greatly increase the cost of providing our product candidates, if approved, or even prevent us from offering our product candidates, if approved, in certain jurisdictions.

Our internal computer systems, or those used by our CROs, CMOs or other contractors or consultants, may fail or suffer security breaches.

Despite the implementation of security measures, our internal computer systems and those of our future CROs, CMOs and other contractors and consultants are vulnerable to damage from computer viruses and unauthorized access. While we have not experienced any such material system failure or security breach to date, if such an event were to occur and cause interruptions in our operations, it could result in a material disruption of our development programs and our business operations. For example, the loss of clinical trial data from completed or future clinical trials could result in delays in our regulatory approval efforts and significantly increase our costs to recover or reproduce the data. Likewise, we currently rely on third parties for the manufacture of our product candidates and to conduct clinical trials, and similar events relating to their computer systems could also have a material adverse effect on our business. To the extent that any disruption or security breach were to result in a loss of, or damage to, our data or applications, or inappropriate disclosure of confidential or proprietary information, we could incur liability and the further development and commercialization of our product candidates could be delayed.

Our employees, independent contractors, consultants, commercial partners and vendors may engage in misconduct or other improper activities, including noncompliance with regulatory standards and requirements.

We are exposed to the risk of employee fraud or other illegal activity by our employees, independent contractors, consultants, commercial partners and vendors. Misconduct by these parties could include intentional, reckless and/or negligent conduct that fails to comply with the laws of the FDA and other similar foreign regulatory bodies, provide true, complete and accurate information to the FDA and other similar foreign regulatory bodies, comply with manufacturing standards we have established, comply with healthcare fraud and abuse laws in the United States and similar foreign fraudulent misconduct laws, or report financial information or data accurately or to disclose unauthorized activities to us. If we obtain FDA approval of any of our product candidates and begin commercializing those products in the United States, our potential exposure under such laws will increase significantly, and our costs associated with compliance with such laws are also likely to increase. These laws may impact, among other things, our current activities with principal investigators and research patients, as well as proposed and future sales, marketing and education programs.

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

Healthcare providers, physicians and third-party payors in the United States and elsewhere play a primary role in the recommendation and prescription of pharmaceutical products. Arrangements with third-party payors and customers can expose pharmaceutical manufactures to broadly applicable fraud and abuse and other healthcare laws and regulations, including, without limitation, the federal Anti-Kickback Statute and the federal False Claims Act, which may constrain the business or financial arrangements and relationships through which such companies sell, market and distribute pharmaceutical products. In particular, the promotion, sales and marketing of healthcare items and services, as well as certain business arrangements in the healthcare industry, are subject to extensive laws designed to prevent fraud, kickbacks, self-dealing and other abusive practices. These laws and regulations may restrict or prohibit a wide range of pricing, discounting, marketing and promotion, structuring and commission(s), certain customer incentive programs and other business arrangements generally. Activities subject to these laws also involve the improper use of information

obtained in the course of patient recruitment for clinical trials. The applicable federal, state and foreign healthcare laws and regulations laws that may affect our ability to operate include, but are not limited to:

- the federal Anti-Kickback Statute, which prohibits, among other things, knowingly and willfully soliciting, receiving, offering or paying any remuneration (including any kickback, bribe or rebate), directly or indirectly, overtly or covertly, in cash or in kind, to induce, or in return for, either the referral of an individual, or the purchase, lease, order or recommendation of any good, facility, item or service for which payment may be made, in whole or in part, under a federal healthcare program, such as the Medicare and Medicaid programs. A person or entity can be found guilty of violating the statute without actual knowledge of the statute or specific intent to violate it. In addition, a claim including items or services resulting from a violation of the federal Anti-Kickback Statute constitutes a false or fraudulent claim for purposes of the False Claims Act, or FCA. The Anti-Kickback Statute has been interpreted to apply to arrangements between pharmaceutical manufacturers on the one hand and prescribers, purchasers, and formulary managers on the other. There are a number of statutory exceptions and regulatory safe harbors protecting some common activities from prosecution;

- federal civil and criminal false claims laws and civil monetary penalty laws, including the FCA, which prohibit, among other things, individuals or entities from knowingly presenting, or causing to be presented, false or fraudulent claims for payment to, or approval by, Medicare, Medicaid, or other federal healthcare programs, knowingly making, using or causing to be made or used a false record or statement material to a false or fraudulent claim or an obligation to pay or transmit money to the federal government, or knowingly concealing or knowingly and improperly avoiding, decreasing or concealing an obligation to pay money to the federal government. Manufacturers can be held liable under the FCA even when they do not submit claims directly to government payors if they are deemed to "cause" the submission of false or fraudulent claims. The FCA also permits a private individual acting as a "whistleblower" to bring actions on behalf of the federal government alleging violations of the FCA and to share in any monetary recovery;

- the federal anti-inducement law, prohibits, among other things, the offering or giving of remuneration, which includes, without limitation, any transfer of items or services for free or for less than fair market value (with limited exceptions), to a Medicare or Medicaid beneficiary that the person knows or should know is likely to influence the beneficiary's selection of a particular supplier of items or services reimbursable by a federal or state governmental program;

- the federal Health Insurance Portability and Accountability Act of 1996, or HIPAA, which created new federal criminal statutes that prohibit knowingly and willfully executing, or attempting to execute, a scheme to defraud any healthcare benefit program or obtain, by means of false or fraudulent pretenses, representations, or promises, any of the money or property owned by, or under the custody or control of, any healthcare benefit program, regardless of the payor (e.g., public or private) and knowingly and willfully falsifying, concealing or covering up by any trick or device a material fact or making any materially false statements in connection with the delivery of, or payment for, healthcare benefits, items or services relating to healthcare matters. Similar to the federal Anti-Kickback Statute, a person or entity can be found guilty of violating HIPAA without actual knowledge of the statute or specific intent to violate it;

- HIPAA, as amended by the Health Information Technology for Economic and Clinical Health Act of 2009, or HITECH, and their respective implementing regulations, which impose, among other things, requirements on certain covered healthcare providers, health plans, and healthcare clearinghouses as well as their respective business associates that perform services for them that involve the use or disclosure of, individually identifiable health information, relating to the privacy, security and transmission of individually identifiable health information without appropriate authorization. HITECH also created new tiers of civil monetary penalties, amended HIPAA to make civil and criminal penalties directly applicable to business associates, and gave state attorneys general new authority to file civil actions for damages or injunctions in federal courts to enforce the federal HIPAA laws and seek attorneys' fees and costs associated with pursuing federal civil actions;

- the federal Physician Payment Sunshine Act, created under the Patient Protection and Affordable Care Act, and its implementing regulations, which require manufacturers of drugs, devices, biologicals and medical supplies for

which payment is available under Medicare, Medicaid or the Children's Health Insurance Program (with certain exceptions) to report annually to the United States Department of Health and Human Services, or HHS, information related to payments or other "transfers of value" made to physicians (defined to include doctors, dentists, optometrists, podiatrists and chiropractors) and teaching hospitals, as well as ownership and investment interests held by physicians and their immediate family members;

- the U.S. Federal Food, Drug, and Cosmetic Act, or FDCA, which prohibits, among other things, the adulteration or misbranding of drugs, biologics and medical devices;

- federal consumer protection and unfair competition laws, which broadly regulate marketplace activities and activities that potentially harm consumers; and

- analogous state and foreign laws and regulations, such as state anti-kickback and false claims laws, which may apply to sales or marketing arrangements and claims involving healthcare items or services reimbursed by non-governmental third-party payors, including private insurers, and may be broader in scope than their federal equivalents; state and foreign laws that require pharmaceutical companies to comply with the pharmaceutical industry's voluntary compliance guidelines and the relevant compliance guidance promulgated by the federal government or otherwise restrict payments that may be made to healthcare providers; state and foreign laws that require drug manufacturers to report information related to payments and other transfers of value to physicians and other healthcare providers or marketing expenditures; and state and foreign laws governing the privacy and security of health information in certain circumstances, many of which differ from each other in significant ways and often are not preempted by HIPAA, thus complicating compliance efforts.

The distribution of pharmaceutical products is subject to additional requirements and regulations, including extensive record-keeping, licensing, storage and security requirements intended to prevent the unauthorized sale of pharmaceutical products.

The scope and enforcement of each of these laws is uncertain and subject to rapid change in the current environment of healthcare reform, especially in light of the lack of applicable precedent and regulations. Federal and state enforcement bodies have recently increased their scrutiny of interactions between healthcare companies and healthcare providers, which has led to a number of investigations, prosecutions, convictions and settlements in the healthcare industry. Ensuring business arrangements comply with applicable healthcare laws, as well as responding to possible investigations by government authorities, can be time- and resource-consuming and can divert a company's attention from the business.

On January 31, 2019, the HHS and HHS Office of Inspector General proposed an amendment to one of the existing Anti-Kickback safe harbors (42 C.F.R. 1001.952(h)) which would prohibit certain pharmaceutical manufacturers from offering rebates to pharmacy benefit managers, or PBMs, in the Medicare Part D and Medicaid managed care programs. The proposed amendment would remove protection for "discounts" from Anti-Kickback enforcement action, and would include criminal and civil penalties for knowingly and willfully offering, paying, soliciting, or receiving remuneration to induce or reward the referral of business reimbursable under federal health care programs. At the same time, HHS also proposed to create a new safe harbor to protect point-of-sale discounts that drug manufacturers provide directly to patients, and adds another safe harbor to protect certain administrative fees paid by manufacturers to PBMs. If this proposal is adopted, in whole or in part, it could affect the pricing and reimbursement for any products for which we receive approval in the future.

The failure to comply with any of these laws or regulatory requirements subjects entities to possible legal or regulatory action. Depending on the circumstances, failure to meet applicable regulatory requirements can result in civil, criminal and administrative penalties, damages, fines, disgorgement, individual imprisonment, possible exclusion from participation in federal and state funded healthcare programs, contractual damages and the curtailment or restricting of our operations, as well as additional reporting obligations and oversight if we become subject to a corporate integrity agreement or other agreement to resolve allegations of non-compliance with these laws. Any action for violation of these laws, even if successfully defended, could cause a pharmaceutical manufacturer to incur significant legal expenses and

divert management's attention from the operation of the business. Prohibitions or restrictions on sales or withdrawal of future marketed products could materially affect business in an adverse way.

We have adopted a code of business conduct and ethics, but it is not always possible to identify and deter employee misconduct, and the precautions we take to detect and prevent inappropriate conduct may not be effective in controlling unknown or unmanaged risks or losses or in protecting us from governmental investigations or other actions or lawsuits stemming from a failure to be in compliance with such laws or regulations. Efforts to ensure that our business arrangements will comply with applicable healthcare laws may involve substantial costs. It is possible that governmental and enforcement authorities will conclude that our business practices may not comply with current or future statutes, regulations or case law interpreting applicable fraud and abuse or other healthcare laws and regulations. If any such actions are instituted against us, and we are not successful in defending ourselves or asserting our rights, those actions could have a significant impact on our business, including the imposition of civil, criminal and administrative penalties, damages, disgorgement, 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 adversely affect our ability to operate our business and our results of operations. In addition, the approval and commercialization of any of our product candidates outside the United States will also likely subject us to foreign equivalents of the healthcare laws mentioned above, among other foreign laws.

We may not be successful in our efforts to identify additional product candidates. Due to our limited resources and access to capital, we must prioritize development of certain product candidates, which may prove to be wrong and may adversely affect our business.

Although we intend to explore other therapeutic opportunities, in addition to the product candidates that we are currently developing, we may fail to identify viable new product candidates for clinical development for a number of reasons. If we fail to identify additional potential product candidates, our business could be materially harmed.

Research programs to pursue the development of our existing and planned product candidates for additional indications and to identify new product candidates and disease targets require substantial technical, financial and human resources whether or not they are ultimately successful. Our research programs may initially show promise in identifying potential indications and/or product candidates, yet fail to yield results for clinical development for a number of reasons, including:

- the research methodology used may not be successful in identifying potential indications and/or product candidates;
- potential product candidates may, after further study, be shown to have harmful adverse effects or other characteristics that indicate they are unlikely to be effective drugs; or
- it may take greater human and financial resources than we will possess to identify additional therapeutic opportunities for our product candidates or to develop suitable potential product candidates through internal research programs, thereby limiting our ability to develop, diversify and expand our product portfolio.

Because we have limited financial and human resources, we intend to initially focus on research programs and product candidates for a limited set of indications. As a result, we may forego or delay pursuit of opportunities with other product candidates or for other indications that later prove to have greater commercial potential or a greater likelihood of success. Our resource allocation decisions may cause us to fail to capitalize on viable commercial products or profitable market opportunities.

Accordingly, there can be no assurance that we will ever be able to identify additional therapeutic opportunities for our product candidates or to develop suitable potential product candidates through internal research programs, which could materially adversely affect our future growth and prospects. We may focus our efforts and resources on potential product candidates or other potential programs that ultimately prove to be unsuccessful.

If we fail to develop additional product candidates, our commercial opportunity will be limited.

Developing and obtaining regulatory approval for and commercializing any additional product candidates we identify will require substantial additional funding beyond the net proceeds from our IPO completed in July 2018 and is prone to the risks of failure inherent in medical product development. We cannot provide you any assurance that we will be able to successfully advance additional product candidates, if any, through the development process.

Even if we receive FDA approval to market additional product candidates for the treatment of the diseases we target, we cannot assure our stockholders that any such product candidates will be successfully commercialized, widely accepted in the marketplace or more effective than other commercially available alternatives. If we are unable to successfully develop and commercialize additional product candidates, our commercial opportunity will be limited. Moreover, a failure in obtaining regulatory approval of additional product candidates may have a negative effect on the approval process of other product candidates of ours or result in losing approval of any approved product candidate.

A variety of risks associated with marketing our product candidates internationally could materially adversely affect our business.

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

- differing regulatory requirements in foreign countries;
- unexpected changes in tariffs, trade barriers, price and exchange controls and other regulatory requirements;
- economic weakness, including inflation, or political instability in particular foreign economies and markets;
- compliance with tax, employment, immigration and labor laws for employees living or traveling abroad;
- foreign taxes, including withholding of payroll taxes;
- foreign currency fluctuations, which could result in increased operating expenses and reduced revenue, and other obligations incident to doing business in another country;
- difficulties staffing and managing foreign operations;
- workforce uncertainty in countries where labor unrest is more common than in the United States;
- potential liability under the Foreign Corrupt Practices Act, or FCPA, or comparable foreign regulations;
- challenges enforcing our contractual and intellectual property rights, especially in those foreign countries that do not respect and protect intellectual property rights to the same extent as the United States;
- production shortages resulting from any events affecting raw material supply or manufacturing capabilities abroad; and
- business interruptions resulting from geo-political actions, including war and terrorism.

These and other risks associated with our international operations may materially adversely affect our ability to attain or maintain profitable operations.

We currently have no marketing and sales organization and have no experience in marketing products. If we are unable to establish marketing and sales capabilities or enter into agreements with third parties to market and sell our product candidates, we may not be able to generate product revenue.

We currently have no sales, marketing or distribution capabilities and have no experience in marketing products. We may develop an in-house marketing organization and sales force, which will require significant capital expenditures, management resources and time. In the event we develop and deploy these capabilities, we will have to compete with other pharmaceutical and biotechnology companies to recruit, hire, train and retain marketing and sales personnel.

In addition to establishing internal sales, marketing and distribution capabilities, we may pursue collaborative arrangements regarding the sales and marketing of our products, however, there can be no assurance that we will be able to establish or maintain such collaborative arrangements, or if we are able to do so, that they will have effective sales forces. Any revenue we receive will depend upon the efforts of such third parties, which may not be successful. We may have little or no control over the marketing and sales efforts of such third parties and our revenue from product sales may be lower than if we had commercialized our product candidates ourselves. We also face competition in our search for third parties to assist us with the sales and marketing efforts of our product candidates.

There can be no assurance that we will be able to develop in-house sales and distribution capabilities or establish or maintain relationships with third-party collaborators to commercialize any product in the United States or overseas.

Comprehensive tax reform legislation could adversely affect our business and financial condition.

On December 22, 2017, President Trump signed into law the Tax Cuts and Jobs Act, or the TCJA, that 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 tax rate of 35% to a flat rate of 21%, limitation of the tax deduction for interest expense to 30% of adjusted earnings (except for certain small businesses), limitation of the deduction for net operating losses to 80% of annual taxable income and elimination of net operating loss carrybacks 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. However, the effect of the TCJA on our business, whether adverse or favorable, is uncertain and may not become evident for some period of time. We urge investors to consult with their legal and tax advisers regarding the implications of the TCJA on an investment in our common stock.

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 U.S. federal and state net operating loss, or NOL, carryforwards of $93.2 million and $93.9 million, respectively, which may be available to offset future taxable income. The federal NOLs include $37.2 million which expire at various dates through 2037 and $56.0 million which carryforward indefinitely. The state NOLs expire at various dates through 2038. As of December 31, 2018, we also had U.S. federal and state research and development tax credit carryforwards of $3.0 million and $1.1 million, respectively, which may be available to offset future tax liabilities and begin to expire in 2034 and 2031, respectively. In addition, in general, under Sections 382 and 383 of the Code and corresponding provisions of state law, a corporation that undergoes an "ownership change" is subject to limitations on its ability to utilize its pre-change net operating loss carryforwards 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, including in connection with our recent private placements, IPO and other transactions. 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 and our ability to utilize NOLs or credits may be impaired. 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. 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 business, technology and industry," 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 NOLs or credits that are subject to limitation by Sections 382 and 383 of the Code. The reduction of the corporate tax rate under the TCJA caused a reduction in the economic benefit of our net operating loss carryforwards and other deferred tax assets available to us. Under the TCJA, net operating loss carryforwards generated after December 31, 2017 will not be subject to expiration.

Unstable market and economic conditions may have serious adverse consequences on our business, financial condition and stock price.

As widely reported, global credit and financial markets have experienced extreme volatility and disruptions in the past several years, including severely diminished liquidity and credit availability, declines in consumer confidence, declines in economic growth, increases in unemployment rates and uncertainty about economic stability. There can be no assurance that deterioration in credit and financial markets and confidence in economic conditions will not occur. Our general business strategy may be adversely affected by any such economic downturn, volatile business environment or continued unpredictable and unstable market conditions. If the current equity and credit markets deteriorate, or do not improve, it may make any necessary debt or equity financing more difficult, more costly, and more dilutive. Failure to secure any necessary financing in a timely manner and on favorable terms could have a material adverse effect on our growth strategy, financial performance and stock price and could require us to delay or abandon clinical development plans. In addition, there is a risk that one or more of our current service providers, manufacturers and other partners may not survive these difficult economic times, which could directly affect our ability to attain our operating goals on schedule and on budget.

As of December 31, 2018, we had cash, cash equivalents and investments of $404.1 million. While we are not aware of any downgrades, material losses, or other significant deterioration in the fair value of our cash equivalents and investments since December 31, 2018, no assurance can be given that further deterioration of the global credit and financial markets would not negatively impact our current portfolio of cash equivalents or our ability to meet our financing objectives. Furthermore, our stock price may decline due in part to the volatility of the stock market and the general economic downturn.

Risks related to government regulation

We are very early in our development efforts. All of our product candidates are still in preclinical development. If we are unable to advance our product candidates to clinical development, obtain regulatory approval and ultimately commercialize our product candidates or experience significant delays in doing so, our business will be materially harmed.

We are very early in our development efforts, and all of our product candidates are still in preclinical development. We have invested substantially all of our efforts and financial resources in the identification and preclinical development of RCTs, including the development of our initial product candidates, RTX-134, RTX-240, and RTX-224. Our ability to generate product revenues, which we do not expect will occur for many years, if ever, will depend on the successful development and eventual commercialization of our product candidates, which may never occur. We currently generate no revenue from sales of any products, and we may never be able to develop or commercialize a marketable product. In addition, certain of our product candidate development programs contemplate the development of companion diagnostics, which are assays or tests to identify an appropriate patient population. Companion diagnostics are subject to regulation as medical devices and must themselves be approved for marketing by the FDA or certain other foreign regulatory agencies before we may commercialize our products. The success of our product candidates will depend on several factors, including the following:

- successful completion of preclinical studies;
- approval of INDs for our planned clinical trials or future clinical trials;

- successful enrollment in, and completion of, clinical trials;
- successful development of companion diagnostics for use with certain of our product candidates;
- receipt of regulatory approvals from applicable regulatory authorities;
- establishing commercial manufacturing capabilities or making arrangements with third-party manufacturers for clinical supply and commercial manufacturing;
- obtaining and maintaining patent and trade secret protection or regulatory exclusivity for our product candidates;
- launching commercial sales of our product candidates, if and when approved, whether alone or in collaboration with others;
- acceptance of the product candidates, if and when approved, by patients, the medical community and third-party payors;
- effectively competing with other therapies;
- obtaining and maintaining third-party insurance coverage and adequate reimbursement;
- enforcing and defending intellectual property rights and claims; and
- maintaining a continued acceptable safety profile of the product candidates following approval.

If we do not achieve one or more of these factors in a timely manner or at all, we could experience significant delays or an inability to successfully commercialize our product candidates, which would materially harm our business. If we do not receive regulatory approvals for our product candidates, we may not be able to continue our operations.

We may rely on third parties to conduct investigator-sponsored clinical trials of our product candidates. Any failure by a third party to meet its obligations with respect to the clinical development of our product candidates may delay or impair our ability to obtain regulatory approval for other product candidates.

We may rely on academic and private non-academic institutions to conduct and sponsor clinical trials relating to our product candidates. We will not control the design or conduct of the investigator-sponsored trials, and it is possible that the FDA or non-U.S. regulatory authorities will not view these investigator-sponsored trials as providing adequate support for future clinical trials, whether controlled by us or third parties, for any one or more reasons, including elements of the design or execution of the trials or safety concerns or other trial results.

Such arrangements will likely provide us certain information rights with respect to the investigator-sponsored trials, including access to and the ability to use and reference the data, including for our own regulatory filings, resulting from the investigator-sponsored trials. However, we would not have control over the timing and reporting of the data from investigator-sponsored trials, nor would we own the data from the investigator-sponsored trials. If we are unable to confirm or replicate the results from the investigator-sponsored trials or if negative results are obtained, we would likely be further delayed or prevented from advancing further clinical development of our product candidates. Further, if investigators or institutions breach their obligations with respect to the clinical development of our product candidates, or if the data proves to be inadequate compared to the first-hand knowledge we might have gained had the investigator-sponsored trials been sponsored and conducted by us, then our ability to design and conduct any future clinical trials ourselves may be adversely affected.

Additionally, the FDA or non-U.S. regulatory authorities may disagree with the sufficiency of our right of reference to the preclinical, manufacturing or clinical data generated by these investigator-sponsored trials, or our interpretation of preclinical, manufacturing or clinical data from these investigator-sponsored trials. If so, the FDA or other non-U.S.

regulatory authorities may require us to obtain and submit additional preclinical, manufacturing, or clinical data before we may initiate our planned trials and/or may not accept such additional data as adequate to initiate our planned trials.

Obtaining and maintaining regulatory approval of our product candidates in one jurisdiction does not mean that we will be successful in obtaining regulatory approval of our product candidates in other jurisdictions.

Obtaining and maintaining regulatory approval of our product candidates in one jurisdiction does not guarantee that we will be able to obtain or maintain regulatory approval in any other jurisdiction, while a failure or delay in obtaining regulatory approval in one jurisdiction may have a negative effect on the regulatory approval process in others. For example, even if the FDA grants marketing approval of a product candidate, comparable regulatory authorities in foreign jurisdictions must also approve the manufacturing, marketing and promotion of the product candidate in those countries. Approval procedures vary among jurisdictions and can involve requirements and administrative review periods different from, and greater than, those in the United States, including additional nonclinical studies or clinical trials as clinical trials conducted in one jurisdiction may not be accepted by regulatory authorities in other jurisdictions. In many jurisdictions outside the United States, a product candidate must be approved for reimbursement before it can be approved for sale in that jurisdiction. In some cases, the price that we intend to charge for our products is also subject to approval.

We may also submit marketing applications in other countries. Regulatory authorities in jurisdictions outside of the United States have requirements for approval of product candidates with which we must comply prior to marketing in those jurisdictions. Obtaining foreign regulatory approvals and compliance with foreign regulatory requirements could result in significant delays, difficulties and costs for us and could delay or prevent the introduction of our products in certain countries. If we fail to comply with the regulatory requirements in international markets and/or receive applicable marketing approvals, our target market will be reduced and our ability to realize the full market potential of our product candidates will be harmed.

If we are not able to obtain, or if there are delays in obtaining, required regulatory approvals for our product candidates, we will not be able to commercialize, or will be delayed in commercializing, our product candidates, and our ability to generate revenue will be materially impaired.

Our product candidates and the activities associated with their development and commercialization, including their design, testing, manufacture, safety, efficacy, recordkeeping, labeling, storage, approval, advertising, promotion, sale, distribution, import and export are subject to comprehensive regulation by the FDA and other regulatory agencies in the United States and by comparable authorities in other countries. Before we can commercialize any of our product candidates, we must obtain marketing approval. We have not received approval to market any of our product candidates from regulatory authorities in any jurisdiction and it is possible that none of our product candidates or any product candidates we may seek to develop in the future will ever obtain regulatory approval. We, as a company, have no experience in filing and supporting the applications necessary to gain regulatory approvals and expect to rely on third-party CROs and/or regulatory consultants to assist us in this process. Securing regulatory approval requires the submission of extensive preclinical and clinical data and supporting information to the various regulatory authorities for each therapeutic indication to establish the drug candidate's safety and efficacy. Securing regulatory approval also requires the submission of information about the drug manufacturing process to, and inspection of manufacturing facilities by, the relevant regulatory authority. Our product candidates may not be effective, may be only moderately effective or may prove to have undesirable or unintended side effects, toxicities or other characteristics that may preclude our obtaining marketing approval or prevent or limit commercial use.

The process of obtaining regulatory approvals, both in the United States and abroad, is expensive, may take many years if additional clinical trials are required, 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. Changes in marketing approval policies during the development period, changes in or the enactment of additional statutes or regulations, or changes in regulatory review for each submitted IND, Premarket Approval, or PMA, BLA or equivalent application types, may cause delays in the approval or rejection of an application. The FDA and comparable authorities in other countries 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. Our product candidates could be delayed in receiving, or fail to receive, regulatory approval for many reasons, including the following:

- the FDA or comparable foreign regulatory authorities may disagree with the design or implementation of our clinical trials;
- we may be unable to demonstrate to the satisfaction of the FDA or comparable foreign regulatory authorities that a drug candidate is safe and effective for its proposed indication or a related companion diagnostic is suitable to identify appropriate patient populations;
- the results of clinical trials may not meet the level of statistical significance required by the FDA or comparable foreign regulatory authorities for approval;
- we may be unable to demonstrate that a product candidate's clinical and other benefits outweigh its safety risks;
- the FDA or comparable foreign regulatory authorities may disagree with our interpretation of data from preclinical studies or clinical trials;
- the data collected from clinical trials of our product candidates may not be sufficient to support the submission of an BLA or other submission or to obtain regulatory approval in the United States or elsewhere;
- the FDA or comparable foreign regulatory authorities may fail to approve the manufacturing processes or facilities of third-party manufacturers with which we contract for clinical and commercial supplies; and
- the approval policies or regulations of the FDA or comparable foreign regulatory authorities may significantly change in a manner rendering our clinical data insufficient for approval.

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

We expect the novel nature of our product candidates to create further challenges in obtaining regulatory approval. As a result, our ability to develop product candidates and obtain regulatory approval may be significantly impacted.

For example, the general approach for FDA approval of a new biologic or drug is for sponsors to seek licensure or approval based on dispositive data from well-controlled, Phase 3 clinical trials of the relevant product candidate in the relevant patient population. Phase 3 clinical trials typically involve hundreds of patients, have significant costs and take years to complete. We believe that we may be able to utilize FDA's accelerated approval program for our product candidates given the limited alternatives for treatments for certain rare diseases, cancer and autoimmune diseases, but the FDA may not agree with our plans.

The FDA may also require a panel of experts, referred to as an Advisory Committee, to deliberate on the adequacy of the safety and efficacy data to support approval. The opinion of the Advisory Committee, although not binding, may have a significant impact on our ability to obtain approval of any product candidates that we develop based on the completed clinical trials.

Moreover, approval of genetic or biomarker diagnostic tests may be necessary in order to advance some of our product candidates to clinical trials or potential commercialization. In the future regulatory agencies may require the development and approval of such tests. Accordingly, the regulatory approval pathway for such product candidates may be uncertain, complex, expensive and lengthy, and approval may not be obtained.

In addition, even if we were to obtain approval, regulatory authorities may approve any of our product candidates for fewer or more limited indications than we request, may not approve the price we intend to charge for our products, may

grant approval contingent on the performance of costly post-marketing clinical trials, or may approve a product candidate with a label that does not include the labeling claims necessary or desirable for the successful commercialization of that product candidate. Any of the foregoing scenarios could materially harm the commercial prospects for our product candidates.

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

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

Undesirable side effects caused by our product candidates could cause us to interrupt, delay or halt preclinical studies or 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 other regulatory authorities. While we have not yet initiated clinical trials for any of our product candidates, as is the case with many treatments for rare diseases, cancer and autoimmune diseases, it is likely that there may be side effects associated with their use. Results of our trials could reveal a high and unacceptable severity and prevalence of these or other side effects. In such an event, our trials could be suspended or terminated and the FDA or comparable foreign regulatory authorities could order us to cease further development of or deny approval of our product candidates for any or all targeted indications. The treatment-related side effects could affect patient recruitment or the ability of enrolled patients to complete the trial or result in potential product liability claims. Any of these occurrences may harm our business, financial condition and prospects significantly.

Further, clinical trials by their nature utilize a sample of the potential patient population. With a limited number of patients and limited duration of exposure, rare and severe side effects of our product candidates may only be uncovered with a significantly larger number of patients exposed to the product candidate. If our product candidates receive marketing approval and we or others identify undesirable side effects caused by such product candidates (or any other similar drugs) after such approval, a number of potentially significant negative consequences could result, including:

- regulatory authorities may withdraw or limit their approval of such product candidates;
- regulatory authorities may require the addition of labeling statements, such as a “boxed” warning or a contraindication;
- we may be required to create a medication guide outlining the risks of such side effects for distribution to patients;
- we may be required to change the way such product candidates are distributed or administered, conduct additional clinical trials or change the labeling of the product candidates;
- regulatory authorities may require a Risk Evaluation and Mitigation Strategy, or REMS, plan to mitigate risks, which could include medication guides, physician communication plans, or elements to assure safe use, such as restricted distribution methods, patient registries and other risk minimization tools;
- we may be subject to regulatory investigations and government enforcement actions;
- we may decide to remove such product candidates from the marketplace;
- we could be sued and held liable for injury caused to individuals exposed to or taking our product candidates; and
- our reputation may suffer.

We believe that any of these events could prevent us from achieving or maintaining market acceptance of the affected product candidates and could substantially increase the costs of commercializing our product candidates, if approved, and significantly impact our ability to successfully commercialize our product candidates and generate revenues.

Breakthrough Therapy Designation, Fast Track Designation or Regenerative Medicine Advanced Therapy Designation by the FDA, even if granted for any of our product candidates, may not lead to a faster development, regulatory review or approval process, and it does not increase the likelihood that any of our product candidates will receive marketing approval in the United States.

We may seek a Breakthrough Therapy Designation for some of our product candidates. A breakthrough therapy is defined as a therapy that is intended, alone or in combination with one or more other therapies, to treat a serious or life-threatening disease or condition, and preliminary clinical evidence indicates that the therapy may demonstrate substantial improvement over existing therapies on one or more clinically significant endpoints, such as substantial treatment effects observed early in clinical development. For therapies that have been designated as breakthrough therapies, interaction and communication between the FDA and the sponsor of the trial can help to identify the most efficient path for clinical development while minimizing the number of patients placed in ineffective control regimens. Therapies designated as breakthrough therapies by the FDA may also be eligible for priority review and accelerated approval. Designation as a breakthrough therapy is within the discretion of the FDA. Accordingly, even if we believe one of our product candidates meets the criteria for designation as a breakthrough therapy, the FDA may disagree and instead determine not to make such designation. In any event, the receipt of a Breakthrough Therapy Designation for a product candidate may not result in a faster development process, review or approval compared to therapies considered for approval under conventional FDA procedures and does not assure ultimate approval by the FDA. In addition, even if one or more of our product candidates qualify as breakthrough therapies, the FDA may later decide that such product candidates no longer meet the conditions for qualification or decide that the time period for FDA review or approval will not be shortened.

We may seek Fast Track Designation for some of our product candidates. If a therapy is intended for the treatment of a serious or life-threatening condition and the therapy demonstrates the potential to address unmet medical needs for this condition, the therapy sponsor may apply for Fast Track Designation. The FDA has broad discretion whether or not to grant this designation, so even if we believe a particular product candidate is eligible for this designation; we cannot assure our stockholers that the FDA would decide to grant it. Even if we do receive Fast Track Designation, we may not experience a faster development process, review or approval compared to conventional FDA procedures. The FDA may withdraw Fast Track Designation if it believes that the designation is no longer supported by data from our clinical development program. Fast Track Designation alone does not guarantee qualification for the FDA's priority review procedures.

We may seek Regenerative Medicine Advanced Therapy, or RMAT, designation for one or more of our product candidates. In 2017, the FDA established the RMAT designation as part of its implementation of the 21st Century Cures Act to expedite review of any drug that meets the following criteria: it qualifies as a RMAT, which is defined as a cell therapy, therapeutic tissue engineering product, human cell and tissue product, or any combination product using such therapies or products, with limited exceptions; it is intended to treat, modify, reverse, or cure a serious or life-threatening disease or condition; and preliminary clinical evidence indicates that the drug has the potential to address unmet medical needs for such a disease or condition. Like Breakthrough Therapy Designation, RMAT designation provides potential benefits that include more frequent meetings with FDA to discuss the development plan for the product candidate, and eligibility for rolling review and priority review. Products granted RMAT designation may also be eligible for accelerated approval on the basis of a surrogate or intermediate endpoint reasonably likely to predict long-term clinical benefit, or reliance upon data obtained from a meaningful number of sites, including through expansion to additional sites. RMAT-designated products that receive accelerated approval may, as appropriate, fulfill their post-approval requirements through the submission of clinical evidence, clinical trials, patient registries, or other sources of real world evidence, such as electronic health records; through the collection of larger confirmatory data sets; or via post-approval monitoring of all patients treated with such therapy prior to approval of the therapy. There is no assurance that we will be able to obtain RMAT designation for any of our product candidates. RMAT designation does not change the FDA's standards for product approval, and there is no assurance that such designation will result in expedited review or approval or that the approved indication will not be narrower than the indication covered by the designation. Additionally, RMAT designation can be revoked if the criteria for eligibility cease to be met as clinical data emerges.

We may seek priority review designation for one or more of our other product candidates, but we might not receive such designation, and even if we do, such designation may not lead to a faster development or regulatory review or approval process.

If the FDA determines that a product candidate offers a treatment for a serious condition and, if approved, the product would provide a significant improvement in safety or effectiveness, the FDA may designate the product candidate for priority review. A priority review designation means that the goal for the FDA to review an application is six months, rather than the standard review period of ten months. We may request priority review for our product candidates. The FDA has broad discretion with respect to whether or not to grant priority review status to a product candidate, so even if we believe a particular product candidate is eligible for such designation or status, the FDA may decide not to grant it. Moreover, a priority review designation does not necessarily result in expedited development or regulatory review or approval process or necessarily confer any advantage with respect to approval compared to conventional FDA procedures. Receiving priority review from the FDA does not guarantee approval within the six-month review cycle or at all.

We may fail to obtain and maintain orphan drug designations from the FDA for our current and future product candidates, as applicable.

Our strategy includes filing for orphan drug designation where available for our product candidates. Under the Orphan Drug Act, the FDA may grant orphan drug designation to a drug or biologic intended to treat a rare disease or condition, which is defined as one occurring in a patient population of fewer than 200,000 in the United States, or a patient population greater than 200,000 in the United States where there is no reasonable expectation that the cost of developing the drug or biologic will be recovered from sales in the United States. In the United States, orphan drug designation entitles a party to financial incentives, such as opportunities for grant funding toward clinical trial costs, tax advantages and user-fee waivers. In addition, if a product that has orphan drug designation subsequently receives the first FDA approval for the disease for which it has such designation, the product is entitled to orphan drug exclusivity, which means that the FDA may not approve any other applications, including a full new drug application, or NDA, or BLA, to market the same drug or biologic for the same indication for seven years, except in limited circumstances, such as a showing of clinical superiority to the product with orphan drug exclusivity or where the original manufacturer is unable to assure sufficient product quantity.

In addition, exclusive marketing rights in the United States may be limited if we seek approval for an indication broader than the orphan-designated indication or may be lost if the FDA later determines that the request for designation was materially defective or if we are unable to assure sufficient quantities of the product to meet the needs of patients with the orphan-designated disease or condition. Further, even if we obtain orphan drug exclusivity for a product, that exclusivity may not effectively protect the product from competition because different drugs with different active moieties may receive and be approved for the same condition, and only the first applicant to receive approval will receive the benefits of marketing exclusivity. Even after an orphan-designated product is approved, the FDA can subsequently approve a later drug with the same active moiety for the same condition if the FDA concludes that the later drug is clinically superior if it is shown to be safer, more effective or makes a major contribution to patient care. Orphan drug designation neither shortens the development time or regulatory review time of a drug, nor gives the drug any advantage in the regulatory review or approval process. In addition, while we may seek orphan drug designation for our product candidates, we may never receive such designations.

Even if we receive regulatory approval of any product candidates or therapies, we will be subject to ongoing regulatory obligations and continued regulatory review, which may result in significant additional expense and we may be subject to penalties if we fail to comply with regulatory requirements or experience unanticipated problems with our product candidates.

If any of our product candidates are approved, they will be subject to ongoing regulatory requirements for manufacturing, labeling, packaging, storage, advertising, promotion, sampling, record-keeping, export, import, conduct of post-marketing studies and submission of safety, efficacy and other post-market information, including both federal and state requirements in the United States and requirements of comparable foreign regulatory authorities. In addition,

we will be subject to continued compliance with cGMP and GCP requirements for any clinical trials that we conduct post-approval.

Manufacturers and manufacturers' facilities are required to comply with extensive FDA, and comparable foreign regulatory authority requirements, including ensuring that quality control and manufacturing procedures conform to cGMP regulations. As such, we and our contract manufacturers will be subject to continual review and inspections to assess compliance with cGMP and adherence to commitments made in any BLA, other marketing application, and previous responses to inspection observations. Accordingly, we and others with whom we work must continue to expend time, money, and effort in all areas of regulatory compliance, including manufacturing, production and quality control.

Any regulatory approvals that we receive for our product candidates may be subject to limitations on the approved indicated uses for which the product may be marketed or to the conditions of approval, or contain requirements for potentially costly post-marketing testing, including Phase 4 clinical trials and surveillance to monitor the safety and efficacy of the product candidate. The FDA may also require a risk evaluation and mitigation strategies, or REMS, program as a condition of approval of our product candidates, which could entail requirements for long-term patient follow-up, a medication guide, physician communication plans or additional elements to ensure safe use, such as restricted distribution methods, patient registries and other risk minimization tools. In addition, if the FDA or a comparable foreign regulatory authority approves our product candidates, we will have to comply with requirements including submissions of safety and other post-marketing information and reports and registration.

The FDA may impose consent decrees or withdraw 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 our product candidates, including adverse events of unanticipated severity or frequency, or with our third-party manufacturers or 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 restrictions or other restrictions under a REMS program. Other potential consequences include, among other things:

- restrictions on the marketing or manufacturing of our products, withdrawal of the product from the market or voluntary or mandatory product recalls;
- fines, warning letters or holds on clinical trials;
- refusal by the FDA to approve pending applications or supplements to approved applications filed by us or suspension or revocation of license approvals;
- product seizure or detention or refusal to permit the import or export of our product candidates; and
- 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. Products 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. 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. If we are slow or unable to adapt to changes in existing requirements or the adoption of new requirements or policies, or if we are not able to maintain regulatory compliance, we may lose any marketing approval that we may have obtained which would adversely affect our business, prospects and ability to achieve or sustain profitability.

We also 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. It is difficult to predict how these executive actions, including any executive orders, 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.

Healthcare insurance coverage and reimbursement may be limited or unavailable in certain market segments for our product candidates, if approved, which could make it difficult for us to sell any product candidates or therapies profitably.

The success of our product candidates, if approved, depends on the availability of adequate coverage and reimbursement from third-party payors. In addition, because our product candidates represent new approaches to the treatment of the diseases they target, we cannot be sure that coverage and reimbursement will be available for, or accurately estimate the potential revenue from, our product candidates or assure that coverage and reimbursement will be available for any product that we may develop.

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. Adequate coverage and reimbursement from governmental healthcare programs, such as Medicare and Medicaid, and commercial payors are critical to new product acceptance.

Government authorities and third-party payors, such as private health insurers and health maintenance organizations, decide which drugs and treatments they will cover and the amount of reimbursement. Coverage and reimbursement by a third-party payor may depend upon a number of factors, including the third-party payor's determination that use of a product is:

- a covered benefit under its health plan;
- safe, effective and medically necessary;
- appropriate for the specific patient;
- cost-effective; and
- neither experimental nor investigational.

In the United States, no uniform policy of coverage and reimbursement for products exists among third-party payors. As a result, obtaining coverage and reimbursement approval of a product from a government or other third-party payor is a time-consuming and costly process that could require us to provide to each payor supporting scientific, clinical and cost-effectiveness data for the use of our products on a payor-by-payor basis, with no assurance that coverage and adequate reimbursement will be obtained. Even if we obtain coverage for a given product, the resulting reimbursement payment rates might not be adequate for us to achieve or sustain profitability or may require co-payments that patients find unacceptably high. Further, even if one payor provides coverage for a given product, other payors may not provide coverage for that product. Additionally, third-party payors may not cover, or provide adequate reimbursement for, long-term follow-up evaluations required following the use of product candidates. Patients are unlikely to use our product candidates unless coverage is provided and reimbursement is adequate to cover a significant portion of the cost of our product candidates. Because our product candidates may have a higher cost of goods than conventional therapies, and may require long-term follow-up evaluations, the risk that coverage and reimbursement rates may be inadequate for us to achieve profitability may be greater. There is significant uncertainty related to insurance coverage and reimbursement of newly approved products. It is difficult to predict at this time what third-party payors will decide with respect to the coverage and reimbursement for our product candidates.

Payment methodologies may be subject to changes in healthcare legislation and regulatory initiatives. For example, the Middle Class Tax Relief and Job Creation Act of 2012 required that the Centers for Medicare & Medicaid Services, the

agency responsible for administering the Medicare program, or CMS, reduce the Medicare clinical laboratory fee schedule by 2% in 2013, which served as a base for 2014 and subsequent years. In addition, effective January 1, 2014, CMS also began bundling the Medicare payments for certain laboratory tests ordered while a patient received services in a hospital outpatient setting. Additional state and federal healthcare reform measures are expected to be adopted in the future, any of which could limit the amounts that federal and state governments will pay for healthcare products and services, which could result in reduced demand for certain pharmaceutical products or additional pricing pressures.

Moreover, increasing efforts by governmental and third-party payors in the United States and abroad to cap or reduce healthcare costs may cause such organizations to limit both coverage and the level of reimbursement for newly approved products and, as a result, they may not cover or provide adequate payment for our product candidates. There has been increasing legislative and enforcement interest in the United States with respect to specialty drug pricing practices. Specifically, there have been several recent U.S. Congressional inquiries and proposed federal and state legislation designed to, among other things, bring more transparency to drug pricing, reduce the cost of prescription drugs under Medicare, review the relationship between pricing and manufacturer patient programs, and reform government program reimbursement methodologies for drugs. For example, in October 2017, California became the first state to pass legislation requiring pharmaceutical manufacturers to announce planned drug price increases. While this legislation does not directly affect drug prices, it puts further pressure on pharmaceutical manufacturers in setting prices. At least one state, Oregon, has recently passed a similar law, requiring pharmaceutical manufacturers to disclose cost components, and other states are likely to follow. Additionally, the Trump administration recently released a "Blueprint", or plan, 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. At the state level, legislatures are increasingly passing legislation and implementing regulations designed to control pharmaceutical and biological product pricing, including price or patient reimbursement constraints, discounts, restrictions on certain product access and marketing cost disclosure and transparency measures, and, in some cases, designed to encourage importation from other countries and bulk purchasing. We expect to experience pricing pressures in connection with the sale of any of our product candidates due to the trend toward managed healthcare, the increasing influence of health maintenance organizations, cost containment initiatives and additional legislative changes.

Ongoing healthcare legislative and regulatory reform measures may have a material adverse effect on our business and results of operations.

Changes in regulations, statutes or the interpretation of existing regulations could impact our business in the future by requiring, for example: (i) changes to our manufacturing arrangements; (ii) additions or modifications to product labeling; (iii) the recall or discontinuation of our products; or (iv) additional record-keeping requirements. If any such changes were to be imposed, they could adversely affect the operation of our business.

In the United States, there have been and continue to be a number of legislative initiatives to contain healthcare costs. For example, in March 2010, the Patient Protection and Affordable Care Act, or the ACA, was passed, which substantially changes the way healthcare is financed by both governmental and private insurers, and significantly impacts the U.S. pharmaceutical industry. The ACA, among other things, subjects biological products to potential competition by lower-cost biosimilars, addresses 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, increases the minimum Medicaid rebates owed by manufacturers under the Medicaid Drug Rebate Program and extends the rebate program to individuals enrolled in Medicaid managed care organizations, establishes annual fees and taxes on manufacturers of certain branded prescription drugs, and creates 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 drugs to eligible beneficiaries during their coverage gap period, as a condition for the manufacturer's outpatient drugs to be covered under Medicare Part D.

Since January 2017, President Trump has signed two Executive Orders designed to delay the implementation of certain provisions of the ACA or otherwise circumvent some of the requirements for health insurance mandated by the ACA. One Executive Order directs federal agencies with authorities and responsibilities under the ACA to waive, defer, grant exemptions from, or delay the implementation of any provision of the ACA that would impose a fiscal or regulatory burden on states, individuals, healthcare providers, health insurers, or manufacturers of pharmaceuticals or medical

devices. The second Executive Order terminates the cost-sharing subsidies that reimburse insurers under the ACA. On June 14, 2018, U.S. Court of Appeals for the Federal Circuit ruled that the federal government was not required to pay more than $12 billion in ACA risk corridor payments to third-party payors who argued were owed to them. The effects of this gap in reimbursement on third-party payors, the viability of the ACA marketplace, providers, and potentially our business, are not yet known.

Moreover, on May 30, 2018, the Right to Try Act, was signed into law. The law, among other things, provides a federal framework for certain patients to access certain investigational new drug products that have completed a Phase I clinical trial and that are undergoing investigation for FDA approval. Under certain circumstances, eligible patients can seek treatment without enrolling in clinical trials and without obtaining FDA permission under the FDA expanded access program. There is no obligation for a drug manufacturer to make its drug products available to eligible patients as a result of the Right to Try Act, but the manufacturer must develop an internal policy and respond to patient requests according to that policy. We expect that additional foreign, federal and state healthcare reform measures will be adopted in the future, any of which could limit the amounts that federal and state governments will pay for healthcare products and services, which could result in limited coverage and reimbursement and reduced demand for our products, once approved, or additional pricing pressures.

These laws, and future state and federal healthcare reform measures may be adopted in the future, any of which 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.

European Union drug marketing and reimbursement regulations may materially affect our ability to market and receive coverage for our products in the European member states.

We intend to seek approval to market our product candidates in both the United States and in selected foreign jurisdictions. If we obtain approval in one or more foreign jurisdictions for our product candidates, we will be subject to rules and regulations in those jurisdictions. In some foreign countries, particularly those in the European Union, the pricing of pharmaceutical products is subject to governmental control and other market regulations which could put pressure on the pricing and usage of our product candidates. In these countries, pricing negotiations with governmental authorities can take considerable time after obtaining marketing approval of a product candidate. In addition, market acceptance and sales of our product candidates will depend significantly on the availability of adequate coverage and reimbursement from third-party payors for our product candidates and may be affected by existing and future healthcare reform measures.

Much like the Anti-Kickback Statute prohibition in the United States, 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 also prohibited in the European Union. The provision of benefits or advantages to physicians is governed by the national anti-bribery laws of European Union Member States, such as the UK Bribery Act 2010. Infringement of these laws could result in substantial fines and imprisonment.

Payments made to physicians in certain European Union Member States 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 national laws, industry codes or professional codes of conduct, applicable in the European Union Member States. Failure to comply with these requirements could result in reputational risk, public reprimands, administrative penalties, fines or imprisonment.

In addition, in most foreign countries, including the European Economic Area, the proposed pricing for a drug must be approved before it may be lawfully marketed. The requirements governing drug pricing and reimbursement vary widely from country to country. For example, the European Union provides options for its member states to restrict the range of medicinal products for which their national health insurance systems provide reimbursement and to control the prices of medicinal products for human use. Reference pricing used by various European Union member states and parallel distribution, or arbitrage between low-priced and high-priced member states, can further reduce prices. A member state

may approve a specific price for the medicinal product or it may instead adopt a system of direct or indirect controls on the profitability of the company placing the medicinal product on the market. In some countries, we may be required to conduct a clinical trial 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. 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 of our products. Historically, products launched in the European Union do not follow price structures of the United States and generally prices tend to be significantly lower. 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.

European data collection is governed by restrictive regulations governing the use, processing, and cross-border transfer of personal information.

The collection and use of personal health data in the European Union, or EU, was previously governed by the provisions of the Data Protection Directive, which has been replaced by the GDPR as of May 2018.

The GDPR imposes a broad range of strict requirements on companies subject to the GDPR, such as us, including requirements relating to having legal bases for processing personal information relating to identifiable individuals and transferring such information outside the European Economic Area, or the EEA, including to the United States, providing details to those individuals regarding the processing of their personal information, keeping personal information secure, having data processing agreements with third parties who process personal information, responding to individuals' requests to exercise their rights in respect of their personal information, reporting security breaches involving personal data to the competent national data protection authority and affected individuals, appointing data protection officers, conducting data protection impact assessments, and record-keeping. The GDPR substantially increases the penalties to which we could be subject in the event of any non-compliance, including fines of up to 10 million Euros or up to 2% of our total worldwide annual turnover for certain comparatively minor offenses, or up to 20 million Euros or up to 4% of our total worldwide annual turnover for more serious offenses. Given the new law, we face uncertainty as to the exact interpretation of the new requirements, and we may be unsuccessful in implementing all measures required by data protection authorities or courts in interpretation of the new law.

In particular, national laws of member states of the EU are in the process of being adapted to the requirements under the GDPR, thereby implementing national laws which may partially deviate from the GDPR and impose different obligations from country to country, so that we do not expect to operate in a uniform legal landscape in the EU. Also, in the field of handling genetic data, the GDPR specifically allows national laws to impose additional and more specific requirements or restrictions, and European laws have historically differed quite substantially in this field, leading to additional uncertainty.

If we begin conducting trials in the EEA, we must also ensure that we maintain adequate safeguards to enable the transfer of personal data outside of the EEA, in particular to the United States in compliance with European data protection laws including the GDPR. We expect that we will continue to face uncertainty as to whether our efforts to comply with our obligations under European privacy laws will be sufficient. If we are investigated by a European data protection authority, we may face fines and other penalties. Any such investigation or charges by European data protection authorities could have a negative effect on our existing business and on our ability to attract and retain new clients or pharmaceutical partners. We may also experience hesitancy, reluctance, or refusal by European or multi-national clients or pharmaceutical partners to continue to use our products and solutions due to the potential risk exposure as a result of the current (and, in particular, future) data protection obligations imposed on them by certain data protection authorities in interpretation of current law, including the GDPR. Such clients or pharmaceutical partners may also view any alternative approaches to compliance as being too costly, too burdensome, too legally uncertain, or otherwise objectionable and therefore decide not to do business with us. Any of the foregoing could materially harm our business, prospects, financial condition and results of operations.

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 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 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 the company 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.

We are subject to certain U.S. and foreign anti-corruption, anti-money laundering, export control, sanctions, and other trade laws and regulations. We can face serious consequences for violations.

Among other matters, U.S. and foreign anti-corruption, anti-money laundering, export control, sanctions, and other trade laws and regulations, which are collectively referred to as Trade Laws, prohibit companies and their employees, agents, clinical research organizations, legal counsel, accountants, consultants, contractors, and other partners from authorizing, promising, offering, providing, soliciting, or receiving directly or indirectly, corrupt or improper payments or anything else of value to or from recipients in the public or private sector. Violations of Trade Laws can result in substantial criminal fines and civil penalties, imprisonment, the loss of trade privileges, debarment, tax reassessments, breach of contract and fraud litigation, reputational harm, and other consequences. We have direct or indirect interactions with officials and employees of government agencies or government-affiliated hospitals, universities, and other organizations. We also expect our non-U.S. activities to increase in time. We plan to engage third parties for clinical trials and/or to obtain necessary permits, licenses, patent registrations, and other regulatory approvals and we can be held liable for the corrupt or other illegal activities of our personnel, agents, or partners, even if we do not explicitly authorize or have prior knowledge of such activities.

Inadequate funding for the FDA, the SEC and other government agencies could hinder their ability to hire and retain key leadership and other personnel, prevent new products and services from being developed or commercialized in a timely manner or otherwise prevent those agencies from performing normal business functions on which the operation of our business may rely, which could negatively impact our business.

The ability of the FDA to review and approve new products can be affected by a variety of factors, including government budget and funding levels, ability to hire and retain key personnel and accept the payment of user fees, and

statutory, regulatory, and policy changes. Average review times at the agency have fluctuated in recent years as a result. In addition, government funding of the SEC and other government agencies on which our operations may rely, including those that fund research and development activities, is subject to the political process, which is inherently fluid and unpredictable.

Disruptions at the FDA and other agencies may also slow the time necessary for new drugs to be reviewed and/or approved by necessary government agencies, which would adversely affect our business. For example, over the last several years, including most recently from December 22, 2018 to January 25, 2019, the U.S. government has shut down several times and certain regulatory agencies, such as the FDA and the SEC, have had to furlough critical FDA, SEC and other government employees and stop critical activities. If a prolonged government shutdown occurs, it could significantly impact the ability of the FDA to timely review and process our regulatory submissions, which could have a material adverse effect on our business.

Risks related to our intellectual property

If we are unable to obtain and maintain patent protection for any product candidates we develop or for our RED PLATFORM, our competitors could develop and commercialize products or technology similar or identical to ours, and our ability to successfully commercialize any product candidates we may develop, and our technology may be adversely affected.

Our success depends in large part on our ability to obtain and maintain patent protection in the United States and other countries with respect to our product candidates, RED PLATFORM and other technologies we may develop. We seek to protect our proprietary position by in-licensing intellectual property and filing patent applications in the United States and abroad relating to our product candidates and RED PLATFORM, as well as other technologies that are important to our business. Given that the development of our technology and product candidates is at an early stage, our intellectual property portfolio with respect to certain aspects of our technology and product candidates is also at an early stage. For example, we do not own or in-license any issued patents directed to the composition of matter of any of the RCT product candidates that we have thus far developed using our RED PLATFORM. In addition, we do not own or in-license any issued patents covering the methods and processes of our RED PLATFORM. We have filed or intend to file patent applications on these aspects of our technology and our product candidates; however, there can be no assurance that any such patent applications will issue as granted patents. Furthermore, in some cases, we have only filed provisional patent applications on certain aspects of our technology and product candidates and each of these provisional patent applications is not eligible to become an issued patent until, among other things, we file a non-provisional patent application within 12 months of the filing date of the applicable provisional patent application. Any failure to file a non-provisional patent application within this timeline could cause us to lose the ability to obtain patent protection for the inventions disclosed in the associated provisional patent applications.

Composition of matter patents for biological and pharmaceutical products are generally considered to be the strongest form of intellectual property protection for those types of products, as such patents provide protection without regard to any method of use. We cannot be certain, however, that the claims in our pending patent applications covering the composition of matter of our product candidates will be considered patentable by the United States Patent and Trademark Office, or the USPTO, or by patent offices in foreign countries, or that the claims in any of our issued patents will be considered valid and enforceable by courts in the United States or foreign countries. Furthermore, in some cases, we may not be able to obtain issued claims covering compositions of matter relating to our product candidates and RED PLATFORM, as well as other technologies that are important to our business, and instead may need to rely on filing patent applications with claims covering a method of use and/or method of manufacture. Method of use patents protect the use of a product for the specified method. This type of patent does not prevent a competitor from making and marketing a product that is identical to our product for an indication that is outside the scope of the patented method. Moreover, even if competitors do not actively promote their products for our targeted indications, physicians may prescribe these products “off-label” for those uses that are covered by our method of use patents. Although off-label prescriptions may infringe or contribute to the infringement of method of use patents, the practice is common and such infringement is difficult to prevent or prosecute. There can be no assurance that any such patent applications will issue as granted patents, and even if they do issue, such patent claims may be insufficient to prevent third parties, such as our competitors, from utilizing our technology. Any failure to obtain or maintain patent protection with respect to our

product candidates and RED PLATFORM could have a material adverse effect on our business, financial condition, results of operations, and prospects.

If any of our owned or in-licensed patent applications do not issue as patents in any jurisdiction, we may not be able to compete effectively.

Changes in either the patent laws or their interpretation in the United States and other countries may diminish our ability to protect our inventions, obtain, maintain, and enforce our intellectual property rights and, more generally, could affect the value of our intellectual property or narrow the scope of our owned and licensed patents. With respect to our patent portfolio, as of February 28, 2019, all of the patent rights that we own or in-license are currently pending patent applications except that we own one issued U.S. patent directed to methods of treating phenylketonuria with RTX-134. With respect to both in-licensed and owned intellectual property, we cannot predict whether the patent applications we and our licensors are currently pursuing will issue as patents in any particular jurisdiction or whether the claims of any issued patents will provide sufficient protection from competitors or other third parties.

The patent prosecution process is expensive, time-consuming, and complex, and we may not be able to file, prosecute, maintain, enforce, or license all necessary or desirable patents and patent applications at a reasonable cost or in a timely manner. It is also possible that we will fail to identify patentable aspects of our research and development output in time to obtain patent protection. Although we enter into non-disclosure and confidentiality agreements with parties who have access to confidential or patentable aspects of our research and development output, such as our employees, corporate collaborators, outside scientific collaborators, contract research organizations, contract manufacturers, consultants, advisors and other third parties, any of these parties may breach such agreements and disclose such output before a patent application is filed, thereby jeopardizing our ability to seek patent protection. In addition, our ability to obtain and maintain valid and enforceable patents depends on whether the differences between our inventions and the prior art allow our inventions to be patentable over the prior art. Furthermore, publications of discoveries in the scientific literature often lag behind the actual discoveries, and patent applications in the United States and other jurisdictions are typically not published until 18 months after filing, or in some cases not at all. Therefore, we cannot be certain that we or our licensors were the first to make the inventions claimed in any of our owned or licensed patents or pending patent applications, or that we or our licensors were the first to file for patent protection of such inventions.

If the scope of any patent protection we obtain is not sufficiently broad, or if we lose any of our patent protection, our ability to prevent our competitors from commercializing similar or identical technology and product candidates would be adversely affected.

The patent position of biotechnology and pharmaceutical companies generally is highly uncertain, involves complex legal and factual questions, and has been the subject of much litigation in recent years. As a result, the issuance, scope, validity, enforceability, and commercial value of our patent rights are highly uncertain. Our owned or in-licensed pending and future patent applications may not result in patents being issued which protect our product candidates, RED PLATFORM technology, or other technologies or which effectively prevent others from commercializing competitive technologies and product candidates.

No consistent policy regarding the scope of claims allowable in patents in the biotechnology field has emerged in the United States. The patent situation outside of the United States is even more uncertain. Changes in either the patent laws or their interpretation in the United States and other countries may diminish our ability to protect our inventions and enforce our intellectual property rights, and more generally could affect the value of our intellectual property. In particular, our ability to stop third parties from making, using, selling, offering to sell, or importing products that infringe our intellectual property will depend in part on our success in obtaining and enforcing patent claims that cover our technology, inventions and improvements. With respect to both licensed and company-owned intellectual property, we cannot be sure that patents will be granted with respect to any of our pending patent applications or with respect to any patent applications filed by us in the future, nor can we be sure that any of our existing patents or any patents that may be granted to us in the future will be commercially useful in protecting our products and the methods used to manufacture those products. Moreover, even our issued patents do not guarantee us the right to practice our technology in relation to the commercialization of our products. The area of patent and other intellectual property rights in biotechnology is an evolving one with many risks and uncertainties, and third parties may have blocking patents that could be used to

prevent us from commercializing our patented product candidates and practicing our proprietary technology. Our issued patent and those that may issue in the future may be challenged, invalidated, or circumvented, which could limit our ability to stop competitors from marketing related products or limit the length of the term of patent protection that we may have for our product candidates. In addition, the rights granted under any issued patents may not provide us with protection or competitive advantages against competitors with similar technology. Furthermore, our competitors may independently develop similar technologies. For these reasons, we may have competition for our product candidates. Moreover, because of the extensive time required for development, testing and regulatory review of a potential product, it is possible that, before any particular product candidate can be commercialized, any related patent may expire or remain in force for only a short period following commercialization, thereby reducing any advantage of the patent.

Moreover, the coverage claimed in a patent application can be significantly reduced before the patent is issued, and its scope can be reinterpreted after issuance. Even if patent applications we own or license issue as patents, they may not issue in a form that will provide us with any meaningful protection, prevent competitors or other third parties from competing with us, or otherwise provide us with any competitive advantage. Any patents that we own or in-license may be challenged, narrowed, circumvented, or invalidated by third parties. Consequently, we do not know whether our product candidates, RED PLATFORM technologies or other technologies will be protectable or remain protected by valid and enforceable patents. Our competitors or other third parties may be able to circumvent our patents by developing similar or alternative technologies or products in a non-infringing manner which could materially adversely affect our business, financial condition, results of operations and prospects.

The issuance of a patent is not conclusive as to its inventorship, scope, validity, or enforceability, and patents that we own or license may be challenged in the courts or patent offices in the United States and abroad. We or our licensors may be subject to a third party preissuance submission of prior art to the USPTO or to foreign patent authorities or become involved in opposition, derivation, revocation, reexamination, post-grant and *inter partes* review, or interference proceedings or other similar proceedings challenging our owned or licensed patent rights. An adverse determination in any such submission, proceeding or litigation could reduce the scope of, or invalidate or render unenforceable, our owned or in-licensed patent rights, allow third parties to commercialize our product candidates, RED PLATFORM technologies or other technologies and compete directly with us, without payment to us, or result in our inability to manufacture or commercialize products without infringing third-party patent rights. Moreover, we, or one of our licensors, may have to participate in interference proceedings declared by the USPTO to determine priority of invention or in post-grant challenge proceedings, such as oppositions in a foreign patent office, that challenge our or our licensor's priority of invention or other features of patentability with respect to our owned or in-licensed patents and patent applications. Such challenges may result in loss of patent rights, loss of exclusivity, or in patent claims being narrowed, invalidated, or held unenforceable, 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 product candidates, RED PLATFORM and other technologies. Such proceedings also may result in substantial cost and require significant time from our scientists and management, even if the eventual outcome is favorable to us.

In addition, given the amount of time required for the development, testing, and regulatory review of new product candidates, patents protecting such product candidates might expire before or shortly after such product candidates are commercialized. As a result, our intellectual property may not provide us with sufficient rights to exclude others from commercializing products similar or identical to ours.

We may in the future co-own patent rights relating to future product candidates and our RED PLATFORM with third parties. Some of our in-licensed patent rights are, and may in the future be, co-owned with third parties. In addition, our licensors may co-own the patent rights we in-license with other third parties with whom we do not have a direct relationship. Our exclusive rights to certain of these patent rights are dependent, in part, on inter-institutional or other operating agreements between the joint owners of such patent rights, who are not parties to our license agreements. For example, under our license agreement with the Whitehead Institute for Biomedical Research, or WIBR, as amended (or the WIBR License) we license certain patents rights co-owned by WIBR and Tufts University, or Tufts. Our rights to Tufts' interest in such patent rights depends on an inter-institutional agreement between WIBR and Tufts, pursuant to which WIBR controls the licensing of such patent rights. If our licensors do not have exclusive control of the grant of licenses under any such third-party co-owners' interest in such patent rights or we are otherwise unable to secure such exclusive rights, such co-owners may be able to license their rights to other third parties, including our competitors, and

our competitors could market competing products and technology. In addition, we may need the cooperation of any such co-owners of our patent rights in order to enforce such patent rights against third parties, and such cooperation may not be provided to us. Any of the foregoing could have a material adverse effect on our competitive position, business, financial conditions, results of operations, and prospects.

Our rights to develop and commercialize our product candidates and RED PLATFORM are subject, in part, to the terms and conditions of licenses granted to us by others.

We rely upon licenses to certain patent rights and proprietary technology from third parties that are important or necessary to the development of our product candidates and RED PLATFORM. For example, under the WIBR License, WIBR grants us an exclusive, worldwide, sublicensable license under four patent families to research, develop, make, and commercialize products and processes covered by such patent rights for all uses. The portfolio of patent rights licensed to us under the WIBR License is directed, in part, to the *in vitro* production of red blood cells, including the use of the enzyme sortase to conjugate a protein of interest to the cell surface. Patent rights that we in-license may be subject to a reservation of rights by one or more third parties. For example, our in-licensed patent rights from WIBR under the WIBR License were funded in part by the U.S. government. As a result, the U.S. government may have certain rights to such intellectual property. Furthermore, pursuant to a Defense Advanced Research Projects Agency Agreement between WIBR and a global biopharmaceutical company, the biopharmaceutical company funded research resulting in one of the patent families licensed to us under the WIBR License and retained a worldwide, irrevocable, non-exclusive, royalty-free right to use the inventions and technologies covered by this patent family for research and development purposes. WIBR also retains the right with respect to all four patent families licensed to us to (i) to practice the patent rights licensed under the agreement for research, teaching and educational purposes, including sponsored research and collaboration, and (ii) to grant non-exclusive licenses to academic and not-for-profit research institutes to practice under the patent rights for research, teaching and educational purposes (excluding sponsored research), while Tufts retains such rights only with respect to the patent family that it co-owns.

In addition, subject to the terms of any such license agreements, we do not have the right to control the preparation, filing, prosecution and maintenance, and we may not have the right to control the enforcement, and defense of patents and patent applications covering the technology that we license from third parties. For example, under the WIBR License, WIBR controls prosecution of the patent rights licensed to us, and we control enforcement of the patent rights. We cannot be certain that our in-licensed patent applications (and any patents issuing therefrom) that are controlled by our licensors will be prepared, filed, prosecuted, maintained, enforced, and defended in a manner consistent with the best interests of our business. If our licensors fail to prosecute, maintain, enforce, and defend such patents rights, or lose rights to those patent applications (or any patents issuing therefrom), the rights we have licensed may be reduced or eliminated, our right to develop and commercialize any of our product candidates and RED PLATFORM technologies that are subject of such licensed rights could be adversely affected, and we may not be able to prevent competitors from making, using and selling competing products. Moreover, we cannot be certain that such 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 or other intellectual property rights. In addition, even where we have the right to control patent prosecution of patents and patent applications we have licensed to and from third parties, we may still be adversely affected or prejudiced by actions or inactions of our licensees, our licensors and their counsel that took place prior to the date upon which we assumed control over patent prosecution. Finally, subject to the terms of any such license agreements, the licensor may be able to terminate the license without our consent. For example, under the WIBR License, WIBR may terminate the WIBR License upon written notice to us if we, along with our affiliates and sublicensees, cease to carry on business related to the WIBR License for more than six months. WIBR may also terminate the WIBR License for our material breach that remains uncured for sixty days after receiving notice thereof, if we fail to pay amounts due under the agreement within thirty days after receiving notice of such failure, or if we challenge the validity or enforceability of any of the licensed patent rights.

Some intellectual property may have been discovered through government funded programs and thus may be subject to federal regulations such as "march-in" rights, certain reporting requirements and a preference for U.S.-based companies. Compliance with such regulations may limit our exclusive rights, and limit our ability to contract with non-U.S. manufacturers.

Our in licensed patent rights from WIBR under the WIBR License were funded in part by the U.S. government and are therefore subject to certain federal regulations. When new technologies are developed with U.S. government funding, the U.S. government generally obtains certain rights in any resulting patents, including a non-exclusive license authorizing the U.S. government to use the invention or to have others use the invention on its behalf. The U.S. government's rights may also permit it to disclose the funded inventions and technology to third parties and to exercise march in rights to use or allow third parties to use the technology we have licensed that was developed using U.S. government funding. The U.S. government may exercise its march in rights if it determines that action is necessary because we fail to achieve practical application of the government-funded technology, or because action is necessary to alleviate health or safety needs, to meet requirements of federal regulations, or to give preference to U.S. industry. In addition, our rights in such inventions may be subject to certain requirements to manufacture products embodying such inventions in the United States in certain circumstances and if this requirement is not waived. Any exercise by the U.S. government of such rights or by any third party of its reserved rights could have a material adverse effect on our competitive position, business, financial condition, results of operations, and prospects.

If we fail to comply with our obligations in the agreements under which we license intellectual property rights from third parties or otherwise experience disruptions to our business relationships with our licensors, we could lose license rights that are important to our business.

The WIBR License imposes, and we expect our future license agreements will impose, various development, diligence, commercialization, and other obligations on us in order to maintain the licenses. In spite of our efforts, WIBR or a future licensor might conclude that we have materially breached our obligations under such license agreements and seek to terminate the license agreements, thereby removing or limiting our ability to develop and commercialize products and technology covered by these license agreements. If these in-licenses are terminated, or if the underlying patent rights licensed thereunder fail to provide the intended exclusivity, competitors or other third parties would have the freedom to seek regulatory approval of, and to market, products identical to ours and we may be required to cease our development and commercialization of certain of our product candidates or of our current RED PLATFORM technologies. Any of the foregoing could have a material adverse effect on our competitive position, business, financial conditions, results of operations, and prospects.

Moreover, disputes may arise regarding intellectual property subject to a licensing agreement, including:

- the scope of rights granted under the license agreement and other interpretation-related issues;
- the extent to which our technology and processes infringe on intellectual property of the licensor that is not subject to the licensing agreement;
- the sublicensing of patent and other rights under our collaborative development relationships;
- our diligence obligations under the license agreement and what activities satisfy those diligence obligations;
- the inventorship and ownership of inventions and know-how resulting from the joint creation or use of intellectual property by our licensors and us and our partners;
- whether and the extent to which inventors are able to contest the assignment of their rights to our licensors; and
- the priority of invention of patented technology.

The agreements under which we currently license intellectual property or technology from third parties are complex, and certain provisions in such agreements may be susceptible to multiple interpretations. The resolution of any contract

interpretation disagreement that may arise could narrow what we believe to be the scope of our rights to the relevant intellectual property or technology, or increase what we believe to be our financial or other obligations under the relevant agreement, either of which could have a material adverse effect on our business, financial condition, results of operations, and prospects. Moreover, if disputes over intellectual property that we have licensed prevent or impair our ability to maintain our current licensing arrangements on commercially acceptable terms, we may be unable to continue to utilize our RED PLATFORM or successfully develop and commercialize the affected product candidates, which could have a material adverse effect on our business, financial conditions, results of operations, and prospects.

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

Filing, prosecuting, and defending patents on our product candidates, RED PLATFORM technologies and other technologies in all countries throughout the world would be prohibitively expensive, and the laws of foreign countries may not protect our rights to the same extent as the laws of the United States. Consequently, we may not be able to prevent third parties from practicing our inventions in all countries outside the United States, or from selling or importing products made using our inventions in and into the United States or other jurisdictions. Competitors may use our technologies in jurisdictions where we have not obtained patent protection to develop their own products and, further, may export otherwise infringing products to territories where we have patent protection but enforcement is not as strong as that in the United States. These products may compete with our products, and our patents or other intellectual property rights may not be effective or sufficient to prevent them from competing.

Many companies have encountered significant problems in protecting and defending intellectual property rights in foreign jurisdictions. The legal systems of certain countries, particularly certain developing countries, do not favor the enforcement of patents, trade secrets, and other intellectual property protection, particularly those relating to biotechnology products, which could make it difficult for us to stop the infringement of our patents or marketing of competing products in violation of our intellectual property and proprietary rights generally. Proceedings to enforce our intellectual property and proprietary rights in foreign jurisdictions could result in substantial costs and divert our efforts and attention from other aspects of our business, could put our patents at risk of being invalidated or interpreted narrowly, could put our patent applications at risk of not issuing, and could provoke third parties to assert claims against us. We may not prevail in any lawsuits that we initiate, and the damages or other remedies awarded, if any, may not be commercially meaningful. Accordingly, our efforts to enforce our intellectual property and proprietary rights around the world may be inadequate to obtain a significant commercial advantage from the intellectual property that we develop or license.

Many countries have compulsory licensing laws under which a patent owner may be compelled to grant licenses to third parties. In addition, many countries limit the enforceability of patents against government agencies or government contractors. In these countries, the patent owner may have limited remedies, which could materially diminish the value of such patent. If we or any of our licensors is forced to grant a license to third parties with respect to any patents relevant to our business, our competitive position may be impaired, and our business, financial condition, results of operations, and prospects may be adversely affected.

Obtaining and maintaining our patent protection depends on compliance with various procedural, document submission, fee payment, and other requirements imposed by government 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 government fees on patents and applications will be due to be paid to the USPTO and various government patent agencies outside of the United States over the lifetime of our owned or licensed patents and applications. In certain circumstances, we rely on our licensing partners to pay these fees due to U.S. and non-U.S. patent agencies. The USPTO and various non-U.S. government agencies require compliance with several procedural, documentary, fee payment, and other similar provisions during the patent application process. We are also dependent on our licensors to take the necessary action to comply with these requirements with respect to our licensed intellectual property. In some cases, an inadvertent lapse can be cured by payment of a late fee or by other means in accordance with the applicable rules. There are situations, however, in which non-compliance can result in abandonment or lapse of the patent or patent application, resulting in a partial or complete loss of patent rights in the relevant jurisdiction. In such an event, potential competitors might be able to enter the market

with similar or identical products or technology, which could have a material adverse effect on our business, financial condition, results of operations, and prospects.

Changes in U.S. patent law could diminish the value of patents in general, thereby impairing our ability to protect our products.

Changes in either the patent laws or interpretation of the patent laws in the United States could increase the uncertainties and costs surrounding the prosecution of patent applications and the enforcement or defense of issued patents. Assuming that other requirements for patentability are met, prior to March 2013, in the United States, the first to invent the claimed invention was entitled to the patent, while outside the United States, the first to file a patent application was entitled to the patent. After March 2013, under the Leahy-Smith America Invents Act, or the America Invents Act, enacted in September 2011, the United States transitioned to a first inventor to file system in which, assuming that other requirements for patentability are met, the first inventor to file a patent application will be entitled to the patent on an invention regardless of whether a third party was the first to invent the claimed invention. A third party that files a patent application in the USPTO after March 2013, but before us could therefore be awarded a patent covering an invention of ours even if we had made the invention before it was made by such third party. This will require us to be cognizant going forward of the time from invention to filing of a patent application. Since patent applications in the United States and most other countries are confidential for a period of time after filing or until issuance, we cannot be certain that we or our licensors were the first to either (i) file any patent application related to our product candidates, RED PLATFORM or other technologies or (ii) invent any of the inventions claimed in our or our licensor's patents or patent applications.

The America Invents Act also includes a number of significant changes that affect the way patent applications will be prosecuted and also may affect patent litigation. These include allowing third party submission of prior art to the USPTO during patent prosecution and additional procedures to attack the validity of a patent by USPTO administered post-grant proceedings, including post-grant review, *inter partes* review, and derivation proceedings. Because of a lower evidentiary standard in USPTO proceedings compared to the evidentiary standard in United States federal courts necessary to invalidate a patent claim, a third party could potentially provide evidence in a USPTO proceeding sufficient for the USPTO to hold a claim invalid even though the same evidence would be insufficient to invalidate the claim if first presented in a district court action. Accordingly, a third party may attempt to use the USPTO procedures to invalidate our patent claims that would not have been invalidated if first challenged by the third party as a defendant in a district court action. Therefore, the America Invents Act and its implementation could increase the uncertainties and costs surrounding the prosecution of our owned or in-licensed patent applications and the enforcement or defense of our owned or in-licensed issued patents, all of which could have a material adverse effect on our business, financial condition, results of operations, and prospects.

In addition, the patent positions of companies in the development and commercialization of biologics and pharmaceuticals are particularly uncertain. Recent U.S. Supreme Court rulings have narrowed the scope of patent protection available in certain circumstances and weakened the rights of patent owners in certain situations. This combination of events has created uncertainty with respect to the validity and enforceability of patents, once obtained. Depending on future actions by the U.S. Congress, the federal courts, and the USPTO, the laws and regulations governing patents could change in unpredictable ways that could have a material adverse effect on our existing patent portfolio and our ability to protect and enforce our intellectual property in the future.

Issued patents covering our product candidates, and any patents that may issue covering our RED PLATFORM technologies and other technologies, could be found invalid or unenforceable if challenged in court or before administrative bodies in the United States or abroad.

If we or one of our licensors initiated legal proceedings against a third party to enforce a patent covering our product candidates, RED PLATFORM technologies or other technologies, the defendant could counterclaim that such patent is invalid or unenforceable. In patent litigation in the United States, defendant counterclaims alleging invalidity or unenforceability are commonplace. Grounds for a validity challenge could be an alleged failure to meet any of several statutory requirements, including lack of novelty, obviousness or non-enablement. Grounds for an unenforceability assertion could be an allegation that someone connected with prosecution of the patent withheld relevant information

from the USPTO, or made a misleading statement, during prosecution. Third parties may raise claims challenging the validity or enforceability of our owned or in-licensed patents before administrative bodies in the United States or abroad, even outside the context of litigation. Such mechanisms include re-examination, post-grant review, *inter partes* review, interference proceedings, derivation proceedings, and equivalent proceedings in foreign jurisdictions (e.g., opposition proceedings). Such proceedings could result in the revocation of, cancellation of, or amendment to our patents in such a way that they no longer cover our product candidates, RED PLATFORM technologies, or other technologies. The outcome following legal assertions of invalidity and unenforceability is unpredictable. With respect to the validity question, for example, we cannot be certain that there is no invalidating prior art, of which we or our licensing partners and the patent examiner were unaware during prosecution. If a third party were to prevail on a legal assertion of invalidity or unenforceability, we would lose at least part, and perhaps all, of the patent protection on our product candidates, RED PLATFORM or other technologies. Such a loss of patent protection would have a material adverse impact on our business, financial condition, results of operations, and prospects.

If we do not obtain patent term extension and/or data exclusivity for any product candidates we may develop, our business may be materially harmed.

Depending upon the timing, duration and specifics of any FDA marketing approval of any product candidates we may develop, one or more of our owned or in-licensed U.S. patents may be eligible for limited patent term extension under the Hatch-Waxman Act. The Hatch-Waxman Act permits a patent term extension of up to five years as compensation for patent term lost during the FDA regulatory review process. A patent term extension cannot extend the remaining term of a patent beyond a total of 14 years from the date of product approval, only one patent may be extended and only those claims covering the approved drug, a method for using it, or a method for manufacturing it may be extended. Similar extensions as compensation for patent term lost during regulatory review processes are also available in certain foreign countries and territories, such as in Europe under a Supplementary Patent Certificate. However, we may not be granted an extension in the United States and/or foreign countries and territories because of, for example, failing to exercise due diligence during the testing phase or regulatory review process, failing to apply within applicable deadlines, failing to apply prior to expiration of relevant patents, or otherwise failing to satisfy applicable requirements. Moreover, the applicable time period or the scope of patent protection afforded could be less than we request. If we are unable to obtain patent term extension or the term of any such extension is shorter than what we request, our competitors may obtain approval of competing products following our patent expiration, and our business, financial condition, results of operations and prospects could be materially harmed.

We may be subject to claims challenging the inventorship of our patents and other intellectual property.

We or our licensors may be subject to claims that former employees, collaborators or other third parties have an interest in our owned or in-licensed patent rights, trade secrets, or other intellectual property as an inventor or co-inventor. For example, we or our licensors may have inventorship disputes arise from conflicting obligations of employees, consultants or others who are involved in developing our product candidates, RED PLATFORM or other technologies. Litigation may be necessary to defend against these and other claims challenging inventorship or our licensors' ownership of our owned or in-licensed patent rights, trade secrets or other intellectual property. If we or our licensors fail in defending any such claims, in addition to paying monetary damages, we may lose valuable intellectual property rights, such as exclusive ownership of, or right to use, intellectual property that is important to our product candidates, RED PLATFORM and other technologies. Even if we are successful in defending against such claims, litigation could result in substantial costs and be a distraction to management and other employees. Any of the foregoing could have a material adverse effect on our business, financial condition, results of operations and prospects.

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

In addition to seeking patents for our product candidates, RED PLATFORM and other technologies, we also rely on trade secrets and confidentiality agreements to protect our unpatented know-how, technology, and other proprietary information and to maintain our competitive position. Trade secrets and know-how can be difficult to protect. We expect our trade secrets and know-how to over time be disseminated within the industry through independent development, the

publication of journal articles describing the methodology, and the movement of personnel from academic to industry scientific positions.

We currently, and may continue in the future continue to, rely on third parties to assist us in developing and manufacturing our product candidates. Accordingly, we must, at times, share know-how and trade secrets, including those related to our RED PLATFORM, with them. We may in the future also enter into research and development collaborations with third parties that may require us to share know-how and trade secrets under the terms of our research and development partnerships or similar agreements. We seek to protect our know-how, trade secrets and other proprietary technology, in part, by entering into non-disclosure and confidentiality agreements, and including in our vendor and service agreements terms protecting our confidential information, know-how and trade secrets, with parties who have access to such information, such as our employees, scientific collaborators, contract research organizations, contract manufacturers, consultants, advisors and other third parties. We also enter into confidentiality and invention or patent assignment agreements with our employees and consultants as well as train our employees not to bring or use proprietary information or technology from former employers to us or in their work, and we remind former employees when they leave their employment of their confidentiality obligations. However, we cannot guarantee that we have entered into such agreements with each party that may have or have had access to our trade secrets or proprietary technology and processes. We also seek to preserve the integrity and confidentiality of our data and other confidential information by maintaining physical security of our premises and physical and electronic security of our information technology systems.

Despite our efforts, any of the aforementioned parties may breach the agreements and disclose our proprietary information, including our trade secrets, or there may be a lapses or failures in our physical and electronic security systems which lead to our proprietary information being disclosed, and we may not be able to obtain adequate remedies in the event of any such breaches. Monitoring unauthorized uses and disclosures is difficult, and we do not know whether the steps we have taken to protect our proprietary technologies will be effective. If any of our scientific advisors, employees, contractors and consultants who are parties to these agreements breaches or violates the terms of any of these agreements, we may not have adequate remedies for any such breach or violation, and we could lose our trade secrets as a result. Moreover, if confidential information that is licensed or disclosed to us by our partners, collaborators, or others is inadvertently disclosed or subject to a breach or violation, we may be exposed to liability to the owner of that confidential information. Enforcing a claim that a party illegally disclosed or misappropriated a trade secret is difficult, expensive, and time-consuming, and the outcome is unpredictable. In addition, some courts inside and outside the United States are less willing or unwilling to protect trade secrets. If any of our trade secrets were to be lawfully obtained or independently developed by a competitor or other third party, we would have no right to prevent them from using that technology or information to compete with us. If any of our trade secrets were to be disclosed to or independently developed by a competitor or other third party, our competitive position would be materially and adversely harmed.

We may not be successful in obtaining, through acquisitions, in-licenses or otherwise, necessary rights to our product candidates, RED PLATFORM technologies or other technologies.

We currently have rights to certain intellectual property, through licenses from third parties, to develop our product candidates and RED PLATFORM technologies. Some pharmaceutical companies, biotechnology companies, and academic institutions are competing with us in the field of cellular therapeutics and red cell technologies and may have patents and have filed and are likely filing patent applications potentially relevant to our business. In order to avoid infringing these third-party patents, we may find it necessary or prudent to obtain licenses to such patents from such third party intellectual property holders. We may also require licenses from third parties for certain technologies that we are evaluating for use with our current or future product candidates. However, we may be unable to secure such licenses or otherwise acquire or in-license any compositions, methods of use, processes, or other intellectual property rights from third parties that we identify as necessary for our current or future product candidates and our RED PLATFORM at a reasonable cost or on reasonable terms, if at all. The licensing or acquisition of third party intellectual property rights is a competitive area, and several more established companies may pursue strategies to license or acquire third party intellectual property rights that we may consider attractive or necessary. These established companies may have a competitive advantage over us due to their size, capital resources and greater clinical development and commercialization capabilities. In addition, companies that perceive us to be a competitor may be unwilling to assign or

license rights to us. We also may be unable to license or acquire third party intellectual property rights on terms that would allow us to make an appropriate return on our investment or at all.

If we are unable to successfully obtain rights to required third party intellectual property rights or maintain the existing intellectual property rights we have, we may be required to expend significant time and resources to redesign our technology, product candidates, or the methods for manufacturing them or to develop or license replacement technology, all of which may not be feasible on a technical or commercial basis. If we are unable to do so, we may be unable to develop or commercialize the affected product candidates or continue to utilize our existing RED PLATFORM technology, which could harm our business, financial condition, results of operations, and prospects significantly.

We may be subject to claims that our employees, consultants, or advisors have wrongfully used or disclosed alleged trade secrets of their current or former employers or claims asserting ownership of what we regard as our own intellectual property.

Many of our employees, consultants, and advisors are currently or were previously employed at universities or other biotechnology or pharmaceutical companies, including our licensors, competitors and potential competitors. Although we try to ensure that our employees, consultants, and advisors 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 individuals have used or disclosed intellectual property, including trade secrets or other proprietary information, of any such individual's current or former employer. Litigation may be necessary to defend against these claims. If we fail in defending any such claims, in addition to paying monetary damages, we may lose valuable intellectual property rights or personnel. Even if we are successful in defending against such claims, litigation could result in substantial costs and be a distraction to management.

In addition, while it is our policy to require our employees and contractors who may be involved in the conception or 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, conceives or develops intellectual property that we regard as our own. The assignment of intellectual property rights may not be self-executing, or the assignment agreements may be breached, and we may be forced to bring claims against third parties, or defend claims that they may bring against us, to determine the ownership of what we regard as our intellectual property. Such claims could have a material adverse effect on our business, financial condition, results of operations, and prospects.

Third-party claims of intellectual property infringement, misappropriation or other violation against us, our licensors or our collaborators may prevent or delay the development and commercialization of our product candidates, RED PLATFORM and other technologies.

The field of cellular therapeutics is competitive and dynamic. Due to the focused research and development that is taking place by several companies, including us and our competitors, in this field, the intellectual property landscape is in flux, and it may remain uncertain in the future. As such, there may be significant intellectual property related litigation and proceedings relating to our owned and in-licensed, and other third party, intellectual property and proprietary rights in the future.

Our commercial success depends in part on our, our licensors' and our collaborators' ability to avoid infringing, misappropriating and otherwise violating the patents and other intellectual property rights of third parties. There is a substantial amount of complex litigation involving patents and other intellectual property rights in the biotechnology and pharmaceutical industries, as well as administrative proceedings for challenging patents, including interference, derivation and reexamination proceedings before the USPTO or oppositions and other comparable proceedings in foreign jurisdictions. As discussed above, recently, due to changes in U.S. law referred to as patent reform, new procedures including *inter partes* review and post-grant review have been implemented. As stated above, this reform adds uncertainty to the possibility of challenge to our patents in the future.

Numerous U.S. and foreign issued patents and pending patent applications owned by third parties exist relating to red cell technologies and therapeutic proteins, including enzymes, and in the fields in which we are developing our product candidates. As the biotechnology and pharmaceutical industries expand and more patents are issued, the risk increases that our product candidates, RED PLATFORM technologies and other technologies may give rise to claims of

infringement of the patent rights of others. We cannot assure you that our product candidates, RED PLATFORM technologies and other technologies that we have developed, are developing or may develop in the future will not infringe existing or future patents owned by third parties. We may not be aware of patents that have already been issued and that a third party, for example, a competitor in the fields in which we are developing our product candidates, RED PLATFORM and other technologies might assert are infringed by our current or future product candidates, RED PLATFORM or other technologies, including claims to compositions, formulations, methods of manufacture or methods of use or treatment that cover our product candidates, RED PLATFORM or other technologies.

It is also possible that patents owned by third parties of which we are aware, but which we do not believe are relevant to our product candidates, RED PLATFORM or other technologies, could be found to be infringed by our product candidates, RED PLATFORM or other technologies. In addition, because patent applications can take many years to issue, there may be currently pending patent applications that may later result in issued patents that our product candidates, RED PLATFORM or other technologies may infringe. We cannot provide any assurances that third-party patents do not exist which might be enforced against our current technology, including our RED PLATFORM technologies, manufacturing methods, product candidates, or future methods or products resulting in either an injunction prohibiting our manufacture or future sales, or, with respect to our future sales, an obligation on our part to pay royalties and/or other forms of compensation to third parties, which could be significant.

Third parties may have patents or obtain patents in the future and claim that the manufacture, use or sale of our product candidates, RED PLATFORM or other technologies infringes upon these patents. We are aware of an issued patent outside the United States that is directed to erythrocytes that comprise exogeneous polypeptides. While we believe that we have reasonable defenses against a claim of infringement, including that certain claims in this patent are invalid, there can be no assurance that we will prevail in any such action by the holder of the patent. In the event that any third party claims that we infringe their patents or that we are otherwise employing their proprietary technology without authorization and initiates litigation against us, even if we believe such claims are without merit, a court of competent jurisdiction could hold that such patents are valid, enforceable and infringed by our product candidates, RED PLATFORM or other technologies. In this case, the holders of such patents may be able to block our ability to commercialize the applicable product candidate or technology unless we obtain a license under the applicable patents, or until such patents expire or are finally determined to be held invalid or unenforceable. Such a license may not be available on commercially reasonable terms or at all. Even if we are able to obtain a license, the license would likely obligate us to pay license fees or royalties or both, and the rights granted to us might be non-exclusive, which could result in our competitors gaining access to the same intellectual property. If we are unable to obtain a necessary license to a third-party patent on commercially reasonable terms, we may be unable to commercialize our product candidates, RED PLATFORM, or other technologies, or such commercialization efforts may be significantly delayed, which could in turn significantly harm our business.

Defense of infringement claims, regardless of their merit, would involve substantial litigation expense and would be a substantial diversion of management and other employee resources from our business, and may impact our reputation. In the event of a successful claim of infringement against us, we may be enjoined from further developing or commercializing our infringing product candidates, RED PLATFORM, or other technologies. In addition, we may have to pay substantial damages, including treble damages and attorneys' fees for willful infringement, obtain one or more licenses from third parties, pay royalties and/or redesign our infringing product candidates or technologies, which may be impossible or require substantial time and monetary expenditure. In that event, we would be unable to further develop and commercialize our product candidates, RED PLATFORM, or other technologies, which could harm our business significantly.

Engaging in litigation to defend against third parties alleging that we have infringed, misappropriated or otherwise violated their patents or other intellectual property rights is very expensive, particularly for a company of our size, and time-consuming. Some of our competitors may be able to sustain the costs of litigation or administrative proceedings more effectively than we can because of greater financial resources. Patent litigation and other proceedings may also absorb significant management time. Uncertainties resulting from the initiation and continuation of patent litigation or other proceedings against us could impair our ability to compete in the marketplace. The occurrence of any of the foregoing could have a material adverse effect on our business, financial condition or results of operations.

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

Competitors may infringe our patents or the patents of our licensing partners, or we may be required to defend against claims of infringement. In addition, our patents or the patents of our licensing partners also may become involved in inventorship, priority or validity disputes. To counter or defend against such claims can be expensive and time-consuming. In an infringement proceeding, a court may decide that a patent owned or in-licensed by us is invalid or unenforceable, the other party's use of our patented technology falls under the safe harbor to patent infringement under 35 U.S.C. §271(e)(1), or may refuse to stop the other party from using the technology at issue on the grounds that our owned and in-licensed patents do not cover the technology in question. An adverse result in any litigation proceeding could put one or more of our owned or in-licensed patents at risk of being invalidated or interpreted narrowly. 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 this type of litigation.

Even if resolved in our favor, litigation or other legal proceedings relating to intellectual property claims may cause us to incur significant expenses and could distract our personnel from their normal responsibilities. In addition, there could be public announcements of the results of hearings, motions, or other interim proceedings or developments, and if securities analysts or investors perceive these results to be negative, it could have a substantial adverse effect on the price of our common stock. Such litigation or proceedings could substantially increase our operating losses and reduce the resources available for development activities or any future sales, marketing, or distribution activities. We may not have sufficient financial or other resources to conduct such litigation or proceedings adequately. Some of our competitors may be able to sustain the costs of such litigation or proceedings more effectively than we can because of their greater financial resources and more mature and developed intellectual property portfolios. Uncertainties resulting from the initiation and continuation of patent litigation or other proceedings could have a material adverse effect on our ability to compete in the marketplace.

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

Our registered or unregistered trademarks or trade names may be challenged, infringed, circumvented or declared generic or determined to be infringing on other marks. We may not be able to protect our rights to these trademarks and trade names, which we need to build name recognition among potential partners or customers in our markets of interest. At times, competitors or other third parties may adopt trade names or trademarks similar to ours, thereby impeding our ability to build brand identity and possibly leading to market confusion. If we assert trademark infringement claims, a court may determine that the marks we have asserted are invalid or unenforceable, or that the party against whom we have asserted trademark infringement has superior rights to the marks in question. In this case, we could ultimately be forced to cease use of such trademarks. In addition, there could be potential trade name or trademark infringement claims brought by owners of other registered trademarks or trademarks that incorporate variations of our registered or unregistered trademarks or trade names. Over the long term, if we are unable to establish name recognition based on our trademarks and trade names, then we may not be able to compete effectively and our business may be adversely affected. Our efforts to enforce or protect our proprietary rights related to trademarks, trade secrets, domain names, copyrights or other intellectual property may be ineffective and could result in substantial costs and diversion of resources and could adversely affect our business, financial condition, results of operations and prospects.

Intellectual property rights do not necessarily address all potential threats.

The degree of future protection afforded by our intellectual property rights is uncertain because intellectual property rights have limitations and may not adequately protect our business or permit us to maintain our competitive advantage. For example:

- others may be able to make products that are similar to our product candidates or utilize similar technology but that are not covered by the claims of the patents that we license or may own;

- we, or our current or future licensors or collaborators, might not have been the first to make the inventions covered by the issued patent or pending patent application that we license or own now or in the future;
- we, or our current or future licensors or collaborators, might not have been the first to file patent applications covering certain of our or their inventions;
- others may independently develop similar or alternative technologies or duplicate any of our technologies without infringing our owned or licensed intellectual property rights;
- it is possible that our current or future pending owned or licensed patent applications will not lead to issued patents;
- issued patents that we hold rights to may be held invalid or unenforceable, including as a result of legal challenges by our competitors or other third parties;
- our competitors or other third parties might conduct research and development activities in countries where we do not have patent rights and then use the information learned from such activities to develop competitive products for sale in our major commercial markets;
- we may not develop additional proprietary technologies that are patentable;
- the patents of others may harm our business; and
- we may choose not to file a patent in order to maintain certain trade secrets or know-how, and a third party may subsequently file a patent covering such intellectual property.

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

Risks related to our reliance on third parties

We will rely on third parties to conduct our clinical trials. If these third parties do not successfully carry out their contractual duties or meet expected deadlines or comply with regulatory requirements, we may not be able to obtain regulatory approval of or commercialize any potential product candidates.

We will depend upon third parties, including independent investigators, to conduct our clinical trials under agreements with universities, medical institutions, CROs, strategic partners and others. We expect to have to negotiate budgets and contracts with CROs and trial sites, which may result in delays to our development timelines and increased costs.

We will rely heavily on third parties over the course of our clinical trials, and, as a result, will have limited control over the clinical investigators and limited visibility into their day-to-day activities, including with respect to their compliance with the approved clinical protocol. Nevertheless, we are responsible for ensuring that each of our trials is conducted in accordance with the applicable protocol, legal and regulatory requirements and scientific standards, and our reliance on third parties does not relieve us of our regulatory responsibilities. We and these third parties are required to comply with GCP requirements, which are regulations and guidelines enforced by the FDA and comparable foreign regulatory authorities for product candidates in clinical development. Regulatory authorities enforce these GCP requirements through periodic inspections of trial sponsors, clinical investigators and trial sites. If we or any of these third parties fail to comply with applicable GCP requirements, the clinical data generated in our clinical trials may be deemed unreliable and the FDA or comparable foreign regulatory authorities may require us to suspend or terminate these trials or perform additional nonclinical studies or clinical trials before approving our marketing applications. We cannot be certain that, upon inspection, such regulatory authorities will determine that any of our clinical trials comply with the GCP requirements. In addition, our clinical trials must be conducted with biologic product produced under cGMP requirements and may require a large number of patients.

Our failure or any failure by these third parties to comply with these regulations or to recruit a sufficient number of patients may require us to repeat clinical trials, which would delay the regulatory approval process. Moreover, our business may be implicated if any of these third parties violates federal or state fraud and abuse or false claims laws and regulations or healthcare privacy and security laws.

Any third parties conducting our future clinical trials will not be our employees and, except for remedies that may be available to us under our agreements with such third parties, we cannot control whether or not they devote sufficient time and resources to our ongoing nonclinical and clinical programs. These third parties may also have relationships with other commercial entities, including our competitors, for whom they may also be conducting clinical trials or other product development activities, which could affect their performance on our behalf. If these third parties do not successfully carry out their contractual duties or obligations or meet expected deadlines, if they need to be replaced or if the quality or accuracy of the clinical data they obtain is compromised due to the failure to adhere to our clinical protocols or regulatory requirements or for other reasons, our clinical trials may be extended, delayed or terminated and we may not be able to complete development of, obtain regulatory approval of or successfully commercialize our product candidates. As a result, our financial results and the commercial prospects for our product candidates would be harmed, our costs could increase and our ability to generate revenue could be delayed.

If any of our relationships with these third-party CROs or others terminate, we may not be able to enter into arrangements with alternative CROs or other third parties or to do so on commercially reasonable terms. Switching or adding additional CROs involves additional cost and requires management time and focus. In addition, there is a natural transition period when a new CRO begins work. As a result, delays may occur, which can materially impact our ability to meet our desired clinical development timelines. Though we carefully manage our relationships with our CROs, there can be no assurance that we will not encounter similar challenges or delays in the future or that these delays or challenges will not have a material adverse impact on our business, financial condition and prospects.

We expect to rely on third parties to manufacture our clinical supply of product candidates, and we intend to rely on third parties to produce and process our products, if approved.

We currently rely on outside vendors to supply raw materials and other important components, such as CD34+ precursor cells and lentiviral vectors, that are used to manufacture our product candidates. We have not yet caused any product candidates to be manufactured or processed on a commercial scale and may not be able to do so for any of our product candidates. We will make changes as we work to optimize the manufacturing process for our product candidates, and we cannot be sure that even minor changes in the process will result in therapies that are safe and effective.

The facilities used to manufacture our product candidates must be approved by the FDA or other foreign regulatory agencies pursuant to inspections that will be conducted after we submit an application to the FDA or other foreign regulatory agencies. We do not currently control the manufacturing process of, and are currently completely dependent on, our contract manufacturing partners for compliance with regulatory requirements, known as cGMP requirements, for manufacture of our product candidates. If and when our recently purchased manufacturing facility becomes operational, we will be responsible for compliance with cGMP requirements. If we or our contract manufacturers cannot successfully manufacture in conformance with our specifications and the strict regulatory requirements of the FDA or other regulatory authorities, we and they will not be able to secure and/or maintain regulatory approval for their manufacturing facilities with respect to the manufacture of our product candidates. 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 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.

For more information, see “Risk factors—Risks related to manufacturing and supply” below.

Our future collaborations may be important to our business. If we are unable to maintain any of these collaborations, or if these collaborations are not successful, our business could be adversely affected.

We have limited capabilities for product development and do not yet have any capability for sales, marketing or distribution. Accordingly, we may enter into collaborations with other companies to provide us with important technologies and funding for our programs and technology, and we may receive additional technologies and funding under these and other collaborations in the future. Any future collaborations we enter into, may pose a number of risks, including the following:

- collaborators have significant discretion in determining the efforts and resources that they will apply;
- collaborators may not perform their obligations as expected;
- collaborators may not pursue development and commercialization of any product candidates that achieve regulatory approval or may elect not to continue or renew development or commercialization programs or license arrangements based on clinical trial results, changes in the collaborators' strategic focus or available funding, or external factors, such as a strategic transaction that may 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 products and product candidates if the collaborators believe that the competitive products are more likely to be successfully developed or can be commercialized under terms that are more economically attractive than ours;
- product candidates discovered in collaboration with us may be viewed by our collaborators as competitive with their own product candidates or products, which may cause collaborators to cease to devote resources to the commercialization of our product candidates;
- collaborators may fail to comply with applicable regulatory requirements regarding the development, manufacture, distribution or marketing of a product candidate or product;
- collaborators with marketing and distribution rights to one or more of our product candidates that achieve regulatory approval may not commit sufficient resources to the marketing and distribution of such product or products;
- disagreements with collaborators, including disagreements over proprietary rights, contract interpretation or the preferred course of development, might cause delays or terminations 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;
- if a collaborator of ours is involved in a business combination, the collaborator might deemphasize or terminate the development or commercialization of any product candidate licensed to it by us; and
- collaborations may be terminated by the collaborator, and, if terminated, we could be required to raise additional capital to pursue further development or commercialization of the applicable product candidates.

If our potential future collaborations do not result in the successful discovery, development and commercialization of products or if one of our collaborators terminates its agreement with us, we may not receive any future research funding or milestone or royalty payments under the collaboration. If we do not receive the funding we expect under these agreements, our development of our technology and product candidates could be delayed and we may need additional resources to develop product candidates and our technology. All of the risks relating to product development, regulatory approval and commercialization described in this Annual Report on Form 10-K also apply to the activities of our therapeutic collaborators.

Additionally, if one of our potential future collaborators terminates its agreement with us, we may find it more difficult to attract new collaborators and our perception in the business and financial communities could be adversely affected.

Collaborations are complex and time-consuming to negotiate and document. 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. We face significant competition in seeking appropriate collaborators. Our ability to 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. 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 increase our expenditures to fund 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 or 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, bring them to market and generate revenue from sales of drugs or continue to develop our technology, and our business may be materially and adversely affected.

Risks related to manufacturing and supply

Cell therapies rely on the availability of specialty raw materials, which may not be available to us on acceptable terms or at all.

Our product candidates require certain specialty raw materials, some of which we obtain from small companies with limited resources and experience to support a commercial product. In addition, those suppliers normally support blood-based hospital businesses and generally do not have the capacity to support commercial products manufactured under cGMP by biopharmaceutical firms. The suppliers may be ill-equipped to support our needs, especially in non-routine circumstances like an FDA inspection or medical crisis, such as widespread contamination. We do not currently have contracts in place with all of the suppliers that we may need at any point in time, and if needed, may not be able to contract with them on acceptable terms or at all. Accordingly, we may experience delays in receiving key raw materials to support clinical or commercial manufacturing.

Our product candidates are uniquely manufactured. If we or any of our third-party manufacturers encounter difficulties in manufacturing our product candidates, our ability to provide supply of our product candidates for clinical trials or our products for patients, if approved, could be delayed or stopped, or we may be unable to maintain a commercially viable cost structure.

The manufacturing process used to produce our product candidates is complex and novel and it has not yet been validated for clinical and commercial production. As a result of these complexities, the cost to manufacture our product candidates is higher than traditional small molecule chemical compounds and monoclonal antibodies and the manufacturing process is less reliable and is more difficult to reproduce. Furthermore, our manufacturing process development and scale-up is at an early stage. The actual cost to manufacture and process our product candidates could be greater than we expect and could materially and adversely affect the commercial viability of our product candidates.

Our manufacturing process may be susceptible to logistical issues associated with the collection of hematopoietic precursor cells from donors, procurement of plasmids and lentiviral vectors sourced from various suppliers and shipment to the RCT product candidate manufacturing site as well as shipment of the final product to clinical centers, manufacturing issues associated with interruptions in the manufacturing process, contamination, equipment or reagent failure, improper installation or operation of equipment, vendor or operator error, inconsistency in cell growth, and variability in product characteristics. Even minor deviations from normal manufacturing processes could result in reduced production yields, lot failures, product defects, product recalls, product liability claims and other supply disruptions. If microbial, viral, or other contaminations are discovered in our product candidates or in our manufacturing facilities in which our product candidates are made, production at such manufacturing facilities may be interrupted for an extended period of time to investigate and remedy the contamination. Further, as product candidates are developed through preclinical to late-stage clinical trials toward approval and commercialization, it is common that various aspects of the development program, such as manufacturing methods, are altered along the way in an effort to optimize processes and results. Such changes carry the risk that they will not achieve these intended objectives, and any of these changes could cause our product candidates to perform differently and affect the results of planned clinical trials or other future clinical trials.

Although we continue to optimize our manufacturing process for our RCT product candidates, doing so is a difficult and uncertain task, and there are risks associated with scaling to the level required for advanced clinical trials or commercialization, including, among others, cost overruns, potential problems with process scale-up, process reproducibility, stability issues, lot consistency, and timely availability of reagents and/or raw materials. We ultimately may not be successful in transferring our production system from our contract manufacturer to any manufacturing facilities we establish ourselves, or our contract manufacturer may not have the necessary capabilities to complete the implementation and development process. If we are unable to adequately validate or scale-up the manufacturing process for our product candidates with our current manufacturer, we will need to transfer to another manufacturer and complete the manufacturing validation process, which can be lengthy. If we are able to adequately validate and scale-up the manufacturing process for our product candidates with a contract manufacturer, we will still need to negotiate with such contract manufacturer an agreement for commercial supply and it is not certain we will be able to come to agreement on terms acceptable to us. As a result, we may ultimately be unable to reduce the cost of goods for our product candidates to levels that will allow for an attractive return on investment if and when those product candidates are commercialized.

The manufacturing process for any products that we may develop is subject to the FDA and foreign regulatory authority approval process, and we will need to contract with manufacturers who can meet all applicable FDA and foreign regulatory authority requirements on an ongoing basis. If we or our CMOs are unable to reliably produce products to specifications acceptable to the FDA or other regulatory authorities, we may not obtain or maintain the approvals we need to commercialize such products. Even if we obtain regulatory approval for any of our product candidates, there is no assurance that either we or our CMOs will be able to manufacture the approved product to specifications acceptable to the FDA or other regulatory authorities, to produce it in sufficient quantities to meet the requirements for the potential launch of the product, or to meet potential future demand. Any of these challenges could delay completion of clinical trials, require bridging clinical trials or the repetition of one or more clinical trials, increase clinical trial costs, delay approval of our product candidates, impair commercialization efforts, increase our cost of goods, and have an adverse effect on our business, financial condition, results of operations and growth prospects. Our future success depends on our ability to manufacture our products on a timely basis with acceptable manufacturing costs, while at the same time maintaining good quality control and complying with applicable regulatory requirements, and an inability to do so could have a material adverse effect on our business, financial condition, and results of operations. In addition, we could incur higher manufacturing costs if manufacturing processes or standards change, and we could need to replace, modify, design, or build and install equipment, all of which would require additional capital expenditures. Specifically, because our product candidates may have a higher cost of goods than conventional therapies, the risk that coverage and reimbursement rates may be inadequate for us to achieve profitability may be greater.

We have acquired and are establishing our own manufacturing facility and infrastructure in addition to or in lieu of relying on CMOs for the manufacture of our product candidates, which will be costly, time-consuming, and which may not be successful.

In July 2018, we purchased a 135,000 square foot manufacturing facility located in Smithfield, Rhode Island as an alternative or in addition to our reliance on CMOs for the manufacture of our product candidates. We are in the process of renovating and customizing our manufacturing facility for our use. We expect that development of our own manufacturing facility will provide us with enhanced control of material supply for both clinical trials and commercialization, enable the more rapid implementation of process changes, and allow for better long-term margins. However, we have no experience as a company in developing a manufacturing facility and may never be successful in developing our own manufacturing facility or capability. As a result, we will also need to hire additional personnel to manage our operations and facilities and develop the necessary infrastructure to continue the research and development, and eventual commercialization, if approved, of our product candidates. We, as a company, have no experience in setting up, building or eventually managing a manufacturing facility. If we failed to select the correct location, or if we fail to complete the renovation and customization in an efficient manner, or fail to recruit the required personnel and generally manage our growth effectively, the development and production of our product candidates could be curtailed or delayed. We may establish multiple manufacturing facilities as we expand our commercial footprint to multiple geographies, which may lead to regulatory delays or prove costly. Even if we are successful, our manufacturing capabilities could be affected by cost-overruns, unexpected delays, equipment failures, labor shortages, natural disasters, power failures and numerous other factors that could prevent us from realizing the intended benefits of our manufacturing strategy and have a material adverse effect on our business.

In addition, the FDA, the EMA and other foreign regulatory authorities may require us to submit samples of any lot of any approved product together with the protocols showing the results of applicable tests at any time. Under some circumstances, the FDA, the EMA or other foreign regulatory authorities may require that we not distribute a lot until the relevant agency authorizes its release. Slight deviations in the manufacturing process, including those affecting quality attributes and stability, may result in unacceptable changes in the product that could result in lot failures or product recalls. Lot failures or product recalls could cause us to delay product launches or clinical trials, which could be costly to us and otherwise harm our business, financial condition, results of operations and prospects. Problems in our manufacturing process could restrict our ability to meet market demand for our products.

We also may encounter problems hiring and retaining the experienced scientific, quality-control and manufacturing personnel needed to operate our manufacturing processes, which could result in delays in production or difficulties in maintaining compliance with applicable regulatory requirements.

Any problems in our manufacturing process or facilities could make us a less attractive collaborator for potential partners, including larger pharmaceutical companies and academic research institutions, which could limit our access to additional attractive development programs.

We do not have experience as a company managing a manufacturing facility.

Operating our own manufacturing facility will require significant resources, and we do not have experience as a company in managing a manufacturing facility. In part because of this lack of experience, we cannot be certain that our manufacturing plans will be completed on time, if at all, or if manufacturing of product candidates from our own manufacturing facility for our planned clinical trials will begin or be completed on time, if at all. In part because of our inexperience, we may have unacceptable or inconsistent product quality success rates and yields, and we may be unable to maintain adequate quality control, quality assurance and qualified personnel. In addition, if we switch from our current CMOs to our own manufacturing facility for one or more of our product candidates in the future, we may need to conduct additional preclinical studies to bridge our modified product candidates to earlier versions. Failure to successfully operate our manufacturing facility could adversely affect the commercial viability of our product candidates.

We are dependent on suppliers for some of our components, precursor cells and materials used to manufacture our product candidates.

We currently depend on suppliers for some of the components and precursor cells necessary for our product candidates and our suppliers of precursor cells depend on the availability of human donors. We cannot be sure that these suppliers will remain in business, that they will be able to identify and recruit adequate numbers of donors, that they will be able to meet our supply needs, or that they will not be purchased by one of our competitors or another company that is not interested in continuing to produce these materials for our intended purpose. There are, in general, relatively few alternative sources of supply for these components and precursor cells. These suppliers may be unable or unwilling to meet our future demands for our clinical trials or commercial sale. Establishing additional or replacement suppliers for these components and precursor cells could take a substantial amount of time and it may be difficult to establish replacement suppliers who meet regulatory requirements. Any disruption in supply from a supplier or manufacturing location could lead to supply delays or interruptions which would damage our business, financial condition, results of operations and prospects.

If we are able to find a replacement supplier, the replacement supplier would need to be qualified and may require additional regulatory authority approval, which could result in further delay. While we seek to maintain adequate inventory of the components, precursor cells and other materials used to manufacture our products, any interruption or delay in the supply of components, precursor cells or other materials, or our inability to obtain components, precursor cells or materials from alternate sources at acceptable prices in a timely manner, could impair our ability to meet the demand of our customers and cause them to cancel orders.

In addition, as part of the FDA's approval of our product candidates, we will also require FDA approval of the individual components of our process, which include the manufacturing processes and facilities of our suppliers.

Our reliance on these suppliers subjects us to a number of risks that could harm our business, and financial condition, including, among other things:

- interruption of product candidate or commercial supply resulting from modifications to or discontinuation of a supplier's operations;
- delays in product shipments resulting from uncorrected defects, reliability issues, or a supplier's variation in a component;
- a lack of long-term supply arrangements for key components with our suppliers;
- inability to obtain adequate supply in a timely manner, or to obtain adequate supply on commercially reasonable terms;
- difficulty and cost associated with locating and qualifying alternative suppliers for our components and precursor cells in a timely manner;
- production delays related to the evaluation and testing of products from alternative suppliers, and corresponding regulatory qualifications;
- delay in delivery due to our suppliers prioritizing other customer orders over ours; and
- fluctuation in delivery by our suppliers due to changes in demand from us or their other customers.

If any of these risks materialize, our manufacturing costs could significantly increase and our ability to meet clinical and commercial demand for our products could be impacted.

Risks related to our common stock

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

Our shares of common stock began trading on The NASDAQ Global Select Market on July 18, 2018. Given the limited trading history of our common stock, there is a risk that an active trading market for our shares will not be sustained, which could put downward pressure on the market price of our common stock and thereby affect the ability of our stockholders to sell their shares.

The price of our stock may be volatile, and our stockholders could lose all or part of their investment.

The trading price of our common stock is likely to be highly volatile and could be subject to wide fluctuations in response to various factors, some of which are beyond our control, including limited trading volume. Since our common stock began trading on The Nasdaq Global Select Market on July 18, 2018, our stock price has traded at prices as low as $12.71 per share and as high as $33.01 per share through February 28, 2019. In addition to the factors discussed in this "Risk factors" section and elsewhere in this Annual Report on Form 10-K, these factors include:

- the commencement, enrollment or results of our ongoing and planned clinical trials of our product candidates or any future clinical trials we may conduct, or changes in the development status of our product candidates;
- any delay in our regulatory filings for our product candidates and any adverse development or perceived adverse development with respect to the applicable regulatory authority's review of such filings;
- adverse results from or delays in clinical trials of our product candidates;
- our decision to initiate a clinical trial, not to initiate a clinical trial or to terminate an existing clinical trial;
- adverse regulatory decisions, including failure to receive regulatory approval of our product candidates;
- changes in laws or regulations applicable to our products, including but not limited to clinical trial requirements for approvals;
- adverse developments concerning our manufacturers;
- our inability to obtain adequate product supply for any approved product or inability to do so at acceptable prices;
- our inability to establish collaborations, if needed;
- our failure to commercialize our product candidates;
- additions or departures of key scientific or management personnel;
- unanticipated serious safety concerns related to the use of our product candidates;
- introduction of new products or services by our competitors;
- announcements of significant acquisitions, strategic partnerships, joint ventures or capital commitments by us or our competitors;
- our ability to effectively manage our growth;
- the size and growth of our initial target markets;

- actual or anticipated variations in quarterly operating results;
- our cash position;
- our failure to meet the estimates and projections of the investment community or that we may otherwise provide to the public;
- publication of research reports about us or our industry, or cellular therapies in particular, or positive or negative recommendations or withdrawal of research coverage by securities analysts;
- changes in the market valuations of similar companies;
- overall performance of the equity markets;
- sales of our common stock by us or our stockholders in the future;
- trading volume of our common stock;
- adoption of new accounting standards;
- ineffectiveness of our internal controls;
- disputes or other developments relating to proprietary rights, including patents, litigation matters and our ability to obtain patent protection for our technologies;
- significant lawsuits, including patent or stockholder litigation;
- general political and economic conditions; and
- other events or factors, many of which are beyond our control.

In addition, the stock market in general, and the market for biopharmaceutical companies in particular, have experienced extreme price and volume fluctuations that have often been unrelated or disproportionate to the operating performance of these companies. Broad market and industry factors may negatively affect the market price of our common stock, regardless of our actual operating performance. If the market price of our common stock does not exceed their purchase price, our stockholders may not realize any return on their investment in us and may lose some or all of their investment. In the past, securities class action litigation has often been instituted against companies following periods of volatility in the market price of a company's securities. This type of litigation, if instituted, could result in substantial costs and a diversion of management's attention and resources, which would harm our business, operating results or financial condition.

We do not intend to pay dividends on our common stock so any returns will be limited to the value of our stock.

We currently anticipate that we will retain future earnings for the development, operation and expansion of our business and do not anticipate declaring or paying any cash dividends for the foreseeable future. Any return to stockholders will therefore be limited in the foreseeable future to the appreciation of their stock.

Our principal stockholders and management own a significant percentage of our stock and will be able to exert significant control over matters subject to stockholder approval.

Our executive officers, directors and their affiliates beneficially hold, in the aggregate, over 50% of our outstanding voting stock. These stockholders will have the ability to influence us through this ownership position. These stockholders may be able to determine all matters requiring stockholder approval. For example, these stockholders may

be able to control elections of directors, amendments of our organizational documents, 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 our stockholders may feel are in their best interest as one of our stockholders.

We are an emerging growth company, and we cannot be certain if the reduced reporting requirements applicable to emerging growth companies will make our common stock less attractive to investors.

We are an emerging growth company, as defined in the Jumpstart Our Business Startups Act, or the JOBS Act, enacted in April 2012. For as long as we continue to be an emerging growth company, we may take advantage of exemptions from various reporting requirements that are applicable to other public companies that are not emerging growth companies, including not being required to comply with the auditor attestation requirements of Section 404 of the Sarbanes-Oxley Act of 2002, as amended, or the Sarbanes-Oxley Act, reduced disclosure obligations regarding executive compensation in our periodic reports and proxy statements and exemptions from the requirements of holding nonbinding advisory votes on executive compensation and stockholder approval of any golden parachute payments not previously approved. We could be an emerging growth company for up to five years following the year in which we completed our IPO, although circumstances could cause us to lose that status earlier. We will remain an emerging growth company until the earlier of (1) the last day of the fiscal year (a) following the fifth anniversary of the completion of our IPO; (b) in which we have total annual gross revenue of at least $1.07 billion; or (c) in which we are deemed to be a large accelerated filer, which requires the market value of our common stock that is held by non-affiliates to exceed $700 million as of the prior June 30th; and (2) the date on which we have issued more than $1.0 billion in non-convertible debt during the prior three-year period. 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 stock price may be more volatile.

Under the JOBS Act, emerging growth companies can also delay adopting new or revised accounting standards until such time as those standards apply to private companies. We have elected not to "opt out" of such extended transition period, which means that when a standard is issued or revised and it has different application dates for public or private companies, we will adopt the new or revised standard at the time private companies adopt the new or revised standard and will do so until such time that we either (i) irrevocably elect to "opt out" of such extended transition period or (ii) no longer qualify as an emerging growth company. This may make comparison of our financial statements with the financial statements of another public company that is not an emerging growth company, or an emerging growth company that has opted out of using the extended transition period, difficult or impossible because of the potential differences in accounting standards used.

We will incur significant 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.

As a public company, we will incur significant legal, accounting and other expenses that we did not incur as a private company. We will be subject to the reporting requirements of the Securities Exchange Act of 1934, as amended, which will require, among other things, that we file with the Securities and Exchange Commission, or the SEC, annual, quarterly and current reports with respect to our business and financial condition. In addition, the Sarbanes-Oxley Act, as well as rules subsequently adopted by the SEC and The Nasdaq Market to implement provisions of the Sarbanes-Oxley Act, impose significant requirements on public companies, including requiring establishment and maintenance of effective disclosure and financial controls and changes in corporate governance practices. Further, in July 2010, the Dodd-Frank Wall Street Reform and Consumer Protection Act, or the Dodd-Frank Act, was enacted. There are significant corporate governance and executive compensation related provisions in the Dodd-Frank Act that require the SEC to adopt additional rules and regulations in these areas, such as "say on pay" and proxy access. Recent legislation permits emerging growth companies to implement many of these requirements over a longer period and up to five years from the pricing of our IPO. We intend to take advantage of this new legislation but cannot guarantee that we will not be required to implement these requirements sooner than budgeted or planned and thereby incur unexpected expenses. Stockholder activism, the current political environment and the current high level of government intervention and regulatory reform may lead to substantial new regulations and disclosure obligations, which may lead to additional compliance costs and impact the manner in which we operate our business in ways we cannot currently anticipate.

We expect the rules and regulations applicable to public companies to substantially increase our legal and financial compliance costs and to make some activities more time-consuming and costly. If these requirements divert the attention of our management and personnel from other business concerns, they could have a material adverse effect on our business, financial condition and results of operations. The increased costs will decrease our net income or increase our net loss, and may require us to reduce costs in other areas of our business or increase the prices of our products or services. For example, we expect these rules and regulations to make it more difficult and more expensive for us to obtain director and officer liability insurance and we may be required to incur substantial costs to maintain the same or similar coverage. We cannot predict or estimate the amount or timing of additional costs we may incur to respond to these requirements. The impact of these requirements could also make it more difficult for us to attract and retain qualified persons to serve on our board of directors, our board committees or as executive officers.

Sales of a substantial number of shares of our common stock by our existing stockholders in the public market could cause our stock price to fall.

In the event a public market for our common stock is sustained in the future, sales of our common stock may be made by holders of our public float or by holders of restricted securities in compliance with the provisions of Rule 144 of the Securities Act of 1933, or the Securities Act. In general, under Rule 144, a non-affiliated person who has satisfied a six-month holding period in a company registered under the Exchange Act, as amended, may, sell their restricted common stock without volume limitation, so long as the issuer is current with all reports under the Exchange Act in order for there to be adequate common public information. Affiliated persons may also sell their common shares held for at least six months, but affiliated persons will be required to meet certain other requirements, including manner of sale, notice requirements and volume limitations. Non-affiliated persons who hold their common shares for at least one year will be able to sell their common stock without the need for there to be current public information in the hands of the public. Future sales of shares of our public float or by restricted common stock made in compliance with Rule 144 may have an adverse effect on the then prevailing market price, if any, of our common stock.

Shares of common stock that are either subject to outstanding options or reserved for future issuance under our existing equity compensation plans will become eligible for sale in the public market to the extent permitted by the provisions of various vesting schedules and Rule 144 and Rule 701 under the Securities Act. If these additional shares of common stock are sold, or if it is perceived that they will be sold, in the public market, the trading price of our common stock could decline. Additionally, the number of shares of our common stock reserved for issuance under our 2018 Stock Option and Incentive Plan will automatically increase each January 1 by 4% of the number of shares of common stock outstanding on the immediately preceding December 31 or such lesser number of shares determined by our compensation committee. Unless our board of directors elects not to increase the number of shares available for future grant each year, our stockholders may experience additional dilution.

The holders of 56,845,438 shares of our common stock, on an as-converted basis, as of February 28, 2019 are entitled to rights with respect to the registration of their shares under the Securities Act. Registration of these shares under the Securities Act would result in the shares becoming freely tradable without restriction under the Securities Act, except for shares held by affiliates, as defined in Rule 144 under the Securities Act. Any sales of securities by these stockholders could have a material adverse effect on the trading price of our common stock.

We have broad discretion in the use of our existing cash, cash equivalents and investments and may not use them effectively.

Our management will have broad discretion in the application of our cash, cash equivalents and investments. Because of the number and variability of factors that will determine our use of our cash, cash equivalents and investments, their ultimate use may vary substantially from their currently intended use. Our management might not apply our cash, cash equivalents and investments in ways that ultimately increase the value of our stockholders investment. The failure by our management to apply these funds effectively could harm our business. Pending their use, we may invest our cash in short-term, investment-grade, interest-bearing securities. These investments may not yield a favorable return to our stockholders. If we do not use our resources in ways that enhance stockholder value, we may fail to achieve expected financial results, which could cause our stock price to decline.

Our operating results may fluctuate significantly, which makes our future operating results difficult to predict and could cause our operating results to fall below expectations or our guidance.

Our quarterly and annual operating results may fluctuate significantly in the future, which makes it difficult for us to predict our future operating results. From time to time, we may enter into license or collaboration agreements with other companies that include development funding and significant upfront and milestone payments and/or royalties, which may become an important source of our revenue. Accordingly, our revenue may depend on development funding and the achievement of development and clinical milestones under current and any potential future license and collaboration agreements and sales of our products, if approved. These upfront and milestone payments may vary significantly from period to period and any such variance could cause a significant fluctuation in our operating results from one period to the next.

In addition, we measure compensation cost for stock-based awards made to employees, directors and non-employee consultants based on the fair value of the award on either the grant date or service completion date, and we recognize the cost as an expense over the recipient's service period. Because the variables that we use as a basis for valuing stock-based awards change over time, including our underlying stock price and stock price volatility, the magnitude of the expense that we must recognize may vary significantly.

Furthermore, our operating results may fluctuate due to a variety of other factors, many of which are outside of our control and may be difficult to predict, including the following:

- the timing and cost of, and level of investment in, research and development activities relating to our current and any future product candidates, which will change from time to time;
- our ability to enroll patients in clinical trials and the timing of enrollment;
- the cost of manufacturing our current and any future product candidates, which may vary depending on FDA guidelines and requirements, the quantity of production and the terms of our agreements with manufacturers;
- the costs associated with our plans to renovate, customize and operate the manufacturing facility we purchased in July 2018 may be greater than we anticipate;
- expenditures that we may incur to acquire or develop additional product candidates and technologies;
- the timing and outcomes of clinical trials for our current product candidates and any other future product candidates or competing product candidates;
- competition from existing and potential future products that compete with our current product candidates and any other future product candidates, and changes in the competitive landscape of our industry, including consolidation among our competitors or partners;
- any delays in regulatory review or approval of our current product candidates or any other future product candidates;
- the level of demand for our current product candidates and any other future product candidates, if approved, which may fluctuate significantly and be difficult to predict;
- the risk/benefit profile, cost and reimbursement policies with respect to our products candidates, if approved, and existing and potential future products that compete with our current product candidates and any other future product candidates;
- our ability to commercialize our current product candidates and any other future product candidates, if approved, inside and outside of the United States, either independently or working with third parties;

- our ability to adequately support future growth;
- potential unforeseen business disruptions that increase our costs or expenses;
- future accounting pronouncements or changes in our accounting policies; and
- the changing and volatile global economic environment.

The cumulative effect of these factors could result in large fluctuations and unpredictability in our quarterly and annual operating results. As a result, comparing our operating results on a period-to-period basis may not be meaningful. Investors should not rely on our past results as an indication of our future performance. This variability and unpredictability could also result in our failing to meet the expectations of industry or financial analysts or investors for any period. If our revenue or operating results fall below the expectations of analysts or investors or below any forecasts we may provide to the market, or if the forecasts we provide to the market are below the expectations of analysts or investors, the price of our common stock could decline substantially. Such a stock price decline could occur even when we have met any previously publicly stated revenue and/or earnings guidance we may provide.

Anti-takeover provisions under our charter documents and Delaware law could delay or prevent a change of control which could limit the market price of our common stock and may prevent or frustrate attempts by our stockholders to replace or remove our current management.

Our amended and restated certificate of incorporation and amended and restated bylaws contain provisions that could delay or prevent a change of control of our company or changes in our board of directors that our stockholders might consider favorable. Some of these provisions include:

- a board of directors divided into three classes serving staggered three-year terms, such that not all members of the board will be elected at one time;
- a prohibition on stockholder action through written consent, which requires that all stockholder actions be taken at a meeting of our stockholders;
- a requirement that special meetings of stockholders be called only by the chairman of the board of directors, the chief executive officer, or by a majority of the total number of authorized directors;
- advance notice requirements for stockholder proposals and nominations for election to our board of directors;
- a requirement that no member of our board of directors may be removed from office by our stockholders except for cause and, in addition to any other vote required by law, upon the approval of not less than two-thirds of all outstanding shares of our voting stock then entitled to vote in the election of directors;
- a requirement of approval of not less than two-thirds of all outstanding shares of our voting stock to amend any bylaws by stockholder action or to amend specific provisions of our certificate of incorporation; and
- the authority of the board of directors to issue preferred stock on terms determined by the board of directors without stockholder approval and which preferred stock may include rights superior to the rights of the holders of common stock.

In addition, because we are incorporated in Delaware, we are governed by the provisions of Section 203 of the Delaware General Corporate Law, which may prohibit certain business combinations with stockholders owning 15% or more of our outstanding voting stock. These anti-takeover provisions and other provisions in our amended and restated certificate of incorporation and amended and restated bylaws could make it more difficult for stockholders or potential acquirers to obtain control of our board of directors or initiate actions that are opposed by the then-current board of directors and could also delay or impede a merger, tender offer or proxy contest involving our company. These provisions could also discourage proxy contests and make it more difficult for our stockholders and other stockholders to elect directors of

their choosing or cause us to take other corporate actions they desire. Any delay or prevention of a change of control transaction or changes in our board of directors could cause the market price of our common stock to decline.

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

The trading market for our common stock will depend in part on the research and reports that securities or industry analysts publish about us or our business. If one or more of the analysts who covers us downgrades our stock or publishes inaccurate or unfavorable research about our business, our stock price may decline. If one or more of these analysts ceases coverage of our company or fails to publish reports on us regularly, demand for our stock could decrease, which might cause our stock price and trading volume to decline.

Our amended and restated bylaws designate specific courts as the exclusive forum for certain litigation that may be initiated by our stockholders, which could limit our stockholders' ability to obtain a favorable judicial forum for disputes with us.

Pursuant to our amended and restated bylaws, unless we consent in writing to the selection of an alternative forum, the Court of Chancery of the State of Delaware (or, if the Chancery Court does not have jurisdiction, the federal district court for the District of Delaware or other state courts of the State of Delaware) is the sole and exclusive forum for (1) any derivative action or proceeding brought on our behalf; (2) any action asserting a claim of breach of a fiduciary duty or other wrongdoing by any of our directors, officers, employees or agents to us or our stockholders; (3) any action asserting a claim against us arising pursuant to any provision of the General Corporation Law of the State of Delaware or our certificate of incorporation or bylaws; (4) any action to interpret, apply, enforce or determine the validity of our certificate of incorporation or bylaws; or (5) any action asserting a claim governed by the internal affairs doctrine. Our amended and restated bylaws further provide that, unless we consent in writing to the selection of an alternative forum, the United States District Court for the District of Massachusetts is the exclusive forum for any private action asserting violations by us or any of our directors or officers of the Securities Act (the "Federal Forum Provision"), or the rules and regulations promulgated thereunder, and of all suits in equity and actions at law brought to enforce any liability or duty created by those statutes or the rules and regulations under such statutes. The forum selection clauses in our amended and restated bylaws may limit our stockholders' ability to obtain a favorable judicial forum for disputes with us.

In *Sciabacucchi v. Salzberg*, C.A. No. 2017-0931-JTL (Del. Ch.), some companies that have adopted similar federal district court forum selection provisions were sued in the Court of Chancery of the State of Delaware by stockholders who assert that those federal district court forum selection provisions are not enforceable. On December 19, 2018, Court of Chancery issued a decision in *Sciabacucchi* declaring that provisions in certificates of incorporation of Delaware companies that purport to require claims under the Securities Act be brought in federal court are ineffective and invalid under Delaware law. On January 17, 2019, the decision was appealed to the Delaware Supreme Court. While the Delaware Supreme Court recently dismissed the appeal on jurisdictional grounds, we expect that the appeal will be re-filed after the Court of Chancery issues a final judgment. Unless and until the Court of Chancery's decision in *Sciabacucchi* is reversed or otherwise abrogated, we do not intend to enforce its Federal Forum Provision designating the District of Massachusetts as the exclusive forum for Securities Act claims. In the event that the Delaware Supreme Court affirms the Court of Chancery's *Sciabacucchi* decision or otherwise makes a determination that provisions such as the Federal Forum Provision are invalid, our Board of Directors intends to amend promptly the Company's bylaws to remove the Federal Forum Provision. Such amendment could cause us to incur additional costs, which could have an adverse effect on our business, financial condition or results of operations.

Item 1B. Unresolved Staff Comments

None.

Item 2. Properties

Our corporate headquarters is located in approximately 85,000 square feet of office and laboratory space at 399 Binney Street, Cambridge, Massachusetts. The lease term for approximately 48,000 square feet commenced on January 28, 2019

and the lease term for the remaining 37,000 square feet is expected to commence in August 2019, following the completion of construction. The lease terms will expire eight and nine years from the commencement date of the 48,000 square feet and the remaining 37,000 square feet, respectively.

In July 2018, we completed the purchase of a 135,000 square foot manufacturing facility located in Smithfield, Rhode Island.

Item 3. Legal Proceedings

We are not currently a party to any material legal proceedings.

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

Certain Information Regarding the Trading of Our Common Stock

Our common stock trades under the symbol "RUBY" on the NASDAQ Global Select Market and has been publicly traded since July 18, 2018. Prior to this time, there was no public market for our common stock.

Holders of Our Common Stock

As of February 28, 2019, there were approximately 51 holders of record of shares of our common stock. This number does not include stockholders for whom shares are held in "nominee" or "street" name.

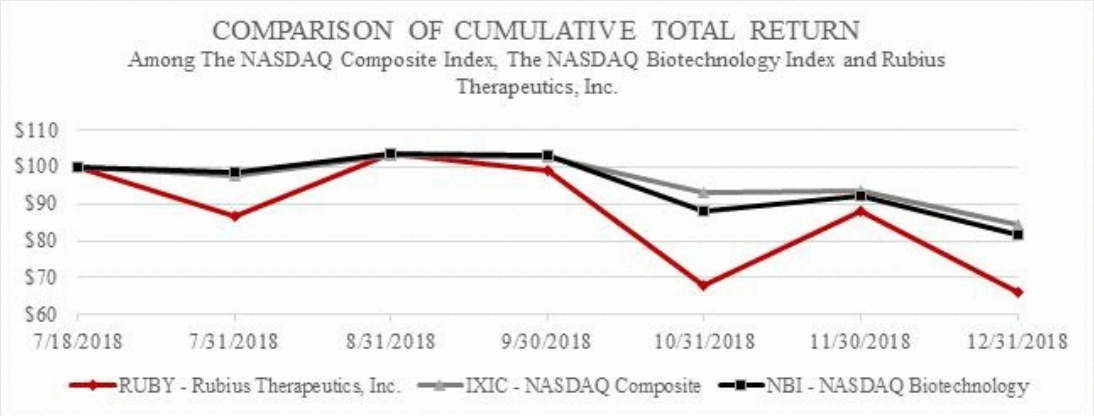
Dividends

We have never declared or paid any cash dividends on our capital stock. We currently intend to retain all available funds and any future earnings for use in the operation of our business and do not anticipate paying any dividends on our common stock in the foreseeable future. Any future determination to declare dividends will be made at the discretion of our board of directors and will depend on our financial condition, operating results, capital requirements, general business conditions and other factors that our board of directors may deem relevant.

Stock Performance Graph

The following performance graph and related information shall not be deemed to be "soliciting material" or to be "filed" with the SEC, for purposes of Section 18 of the Exchange Act, nor shall such information be incorporated by reference into any future filing under the Exchange Act or Securities Act, except to the extent that we specifically incorporate it by reference into such filing.

The following graph compares the performance of our common stock to the NASDAQ Composite Index and to the NASDAQ Biotechnology Index from July 18, 2018 (the first date that shares of our common stock were publicly traded) through December 31, 2018. The comparison assumes $100 was invested in our common stock and in each of the foregoing indices after the market closed on July 18, 2018, and it assumes reinvestment of dividends, if any. The stock price performance included in this graph is not necessarily indicative of future stock price performance.



Securities Authorized for Issuance Under Equity Compensation Plans

Information about our equity compensation plans will be included in our definitive proxy statement to be filed with the SEC with respect to our 2019 Annual Meeting of Stockholders and is incorporated herein by reference.

Unregistered Sales of Equity Securities and Use of Proceeds

Recent Sales of Unregistered Equity Securities

The information required by Item 701 of Regulation S-K was previously included in Quarterly Reports on Form 10-Q filed on August 31, 2018 and November 13, 2018.

Use of Proceeds from Initial Public Offering

On July 20, 2018, we completed the IPO of our common stock pursuant to which we issued and sold 12,055,450 shares of our common stock at a price to the public of $23.00 per share.

The offer and sale of all of the shares of our common stock in our IPO were registered under the Securities Act pursuant to a registration statement on Form S-1, as amended (File No. 333-225840), which was declared effective by the SEC on July 17, 2018 and a registration statement on Form S-1MEF (File No. 333-226214), which was automatically effective upon filing with the SEC on July 17, 2018. Following the sale of all of the shares offered in connection with the closing of our IPO, the offering terminated. J.P. Morgan Securities LLC, Morgan Stanley & Co. LLC, Jefferies LLC and Leerink Partners LLC acted as joint book-running managers of our IPO.

We received aggregate gross proceeds from our IPO of $277.3 million, or aggregate net proceeds of $254.3 million after deducting underwriting discounts and commissions and other offering costs. None of the underwriting discounts and commissions or offering expenses were incurred or paid, directly or indirectly, to directors or officers of ours or their associates or to persons owning 10% or more of our common stock or to any of our affiliates.

As of December 31, 2018, we have used $46.4 million of the net proceeds from the IPO, consisting of $33.5 million used in operations, $8.0 million for the purchase of our manufacturing facility and $4.9 million for the purchase of other property, plant, and equipment. There has been no material change in our planned use of the net proceeds from the IPO as described in our final prospectus filed pursuant to Rule 424(b)(4) under the Securities Act with the SEC on July 18, 2018.

Purchases of Equity Securities by the Issuer and Affiliated Purchasers

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

Item 6. Consolidated Selected Financial Data

You should read the following selected consolidated financial data together with our consolidated financial statements and the related notes appearing at the end of this prospectus and the "Management's discussion and analysis of financial condition and results of operations" section of this prospectus. We have derived the consolidated statements of operations data for the years ended December 31, 2018, 2017 and 2016 and consolidated balance sheet data as of December 31, 2018, 2017 and 2016 from our audited consolidated financial statements appearing at the end of this Annual Report on Form 10-K. We have derived the consolidated balance sheet data as of December 31, 2016 from our audited consolidated financial statements, which are not included in this Annual Report on Form 10-K.Our historical results are not necessarily indicative of the results that may be expected in the future.

	Year Ended December 31,		
	2018	2017	2016
	(in thousands, except share and per share data)		
Consolidated Statements of Operation Data:			
Revenue	$ —	$ —	$ —
Operating expenses:			
Research and development	51,769	21,226	8,403
General and administrative	39,894	22,038	2,449
Total operating expenses	91,663	43,264	10,852
Loss from operations	(91,663)	(43,264)	(10,852)
Other income (expense):			
Change in fair value of preferred stock warrant liability	(2,187)	(785)	1
Interest expense	(464)	(309)	(149)
Interest income and other income (expense), net	5,119	511	(16)
Total other income (expense), net	2,468	(583)	(164)
Net loss	(89,195)	(43,847)	(11,016)
Accretion of Series A redeemable convertible preferred stock to redemption value	—	(656)	(748)
Net loss attributable to common stockholders	$ (89,195)	$ (44,503)	$ (11,764)
Net loss per share attributable to common stockholders, basic and diluted	$ (2.27)	$ (5.55)	$ (1.63)
Weighted average common shares outstanding, basic and diluted	39,285,468	8,023,785	7,200,581

	December 31,		
	2018	2017	2016
	(in thousands)		
Consolidated Balance Sheet Data:			
Cash, cash equivalents and investments	$ 404,051	$ 104,288	$ 6,834
Working capital	394,406	97,830	4,035
Total assets	479,109	107,687	7,989
Long-term debt, net of discount, including current portion	24,347	5,441	3,924
Preferred stock warrant liability	—	866	67
Convertible preferred stock	—	139,790	19,067
Total stockholders' equity (deficit)	393,008	(43,687)	(17,124)

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

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

Overview

We are developing a new class of cellular medicines, Red Cell Therapeutics, or RCTs. Based on our vision that human red blood cells are the foundation of the next significant innovation in medicine, we have designed a proprietary platform to genetically engineer and culture RCTs that are selective, potent and ready-to-use cellular therapies. We believe that our RCTs will provide life-changing or life-saving benefits for patients with severe diseases across multiple therapeutic areas.

We have generated hundreds of RCTs using our RED PLATFORM®, a highly versatile and proprietary cellular therapy platform. We are utilizing our universal engineering and manufacturing processes to advance a broad pipeline of RCT product candidates into clinical trials in rare diseases, cancer and autoimmune diseases. Common design and manufacturing elements of our RCTs should enable us to achieve significant advantages in product development. We are establishing end to end manufacturing capabilities and plan to develop commercial infrastructure to further establish Rubius Therapeutics as a leading, fully integrated cellular therapy company.

Since our inception, we have focused substantially all of our resources on building our proprietary RED PLATFORM, establishing and protecting our intellectual property portfolio, conducting research and development activities, developing our manufacturing process and manufacturing drug product material, organizing and staffing our company, business planning, raising capital and providing general and administrative support for these operations. We do not have any products approved for sale and have not generated any revenue from product sales. To date, we have funded our operations with proceeds from the sale of preferred stock and issuance of debt and, most recently, with proceeds from our initial public offering, or IPO. On July 20, 2018, we completed our IPO, pursuant to which we issued and sold 12,055,450 shares of common stock, inclusive of 1,572,450 shares pursuant to the full exercise of the underwriters' option to purchase additional shares. We received proceeds of $254.3 million after deducting underwriting discounts and commissions and other offering costs. Since our inception, we have incurred significant operating losses. Our ability to generate any product revenue or product revenue sufficient to achieve profitability will depend on the successful development and eventual commercialization of one or more of our product candidates. We reported net losses of $89.2 million for the year ended December 31, 2018, $43.8 million for the year ended December 31, 2017 and $11.0 million for the year ended December 31, 2016. As of December 31, 2018, we had an accumulated deficit of $150.1 million. We expect to continue to incur significant expenses and increasing operating losses for at least the next several years. We expect that our expenses and capital requirements will increase substantially in connection with our ongoing activities, particularly if and as we:

- conduct clinical trials for our product candidates;
- further develop our RED PLATFORM;
- continue to discover and develop additional product candidates;
- maintain, expand and protect our intellectual property portfolio;

- hire additional clinical, scientific manufacturing and commercial personnel;
- expand in-house manufacturing capabilities, including through the renovation, customization and operation of our recently purchased manufacturing facility;
- establish a commercial manufacturing source and secure supply chain capacity sufficient to provide commercial quantities of any product candidates for which we may obtain regulatory approval;
- acquire or in-license other product candidates and technologies;
- seek regulatory approvals for any product candidates that successfully complete clinical trials;
- establish a sales, marketing and distribution infrastructure to commercialize any products for which we may obtain regulatory approval; and
- add operational, financial and management information systems and personnel, including personnel to support our product development and planned future commercialization efforts, as well as to support our transition to a public company.

We will not generate revenue from product sales unless and until we successfully complete clinical development and obtain regulatory approval for our product candidates. If we obtain regulatory approval for any of our product candidates, we expect to incur significant expenses related to developing our commercialization capability to support product sales, marketing and distribution. Further, we expect to incur additional costs associated with operating as a public company.

As a result, we will need substantial additional funding to support our continuing operations and pursue our growth strategy. Until such time as we can generate significant revenue from product sales, if ever, we expect to finance our operations through a combination of equity offerings, debt financings, collaborations, strategic alliances and marketing, distribution or licensing arrangements. We may be unable to raise additional funds or enter into such other agreements or arrangements when needed on favorable terms, or at all. If we fail to raise capital or enter into such agreements as, and when, needed, we may have to significantly delay, scale back or discontinue the development and commercialization of one or more of our product candidates.

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

As of December 31, 2018, we had cash, cash equivalents and investments of $404.1 million. We believe that our existing cash, cash equivalents and investments will enable us to fund our operating expenses, capital expenditure requirements, including the renovation and customization of our recently purchased manufacturing facility, and debt service payments into 2021. See "—Liquidity and Capital Resources."

Components of our Results of Operations

Revenue

To date, we have not generated any revenue from product sales and do not expect to generate any revenue from the sale of products in the near future. If our development efforts for our product candidates are successful and result in regulatory approval or license or collaboration agreements with third parties, we may generate revenue in the future from product sales, payments from collaboration or license agreements that we may enter into with third parties, or any combination thereof.

Operating Expenses

Research and Development Expenses

Research and development expenses consist primarily of costs incurred for our research activities, including our drug discovery efforts, and the development of our product candidates, which include:

- employee-related expenses, including salaries, related benefits and stock-based compensation expense for employees engaged in research and development functions;
- expenses incurred in connection with the preclinical and clinical development of our product candidates and research programs, including under agreements with third parties, such as consultants, contractors and contract research organizations, or CROs;
- the cost of developing and scaling our manufacturing process and manufacturing drug products for use in our preclinical studies and clinical trials, including under agreements with third parties, such as consultants, contractors and contract manufacturing organizations, or CMOs;
- laboratory supplies and research materials;
- facilities, depreciation and other expenses, which include direct and allocated expenses for rent and maintenance of facilities and insurance; and
- payments made under third-party licensing agreements.

We expense research and development costs as incurred. Advance payments that we make for goods or services to be received in the future for use in research and development activities are recorded as prepaid expenses. The prepaid amounts are expensed as the related goods are delivered or the services are performed.

Our direct external research and development expenses are tracked on a program-by-program basis for clinical candidates and consist of costs that include fees, reimbursed materials and other costs paid to consultants, contractors, CMOs and CROs in connection with our preclinical and clinical development and manufacturing activities. We do not allocate employee costs, costs associated with our discovery efforts, laboratory supplies and facilities expenses, including depreciation or other indirect costs, to specific product development programs because these costs are deployed across multiple programs and our platform technology and, as such, are not separately classified.

Product candidates in later stages of clinical development generally have higher development costs than those in earlier stages of clinical development, primarily due to the increased size and duration of later-stage clinical trials. We expect that our research and development expenses will increase substantially in connection with our planned preclinical and clinical development activities in the near term and in the future. At this time, we cannot accurately estimate or know the nature, timing and costs of the efforts that will be necessary to complete the preclinical and clinical development of any of our product candidates. The successful development and commercialization of our product candidates is highly uncertain. This is due to the numerous risks and uncertainties associated with product development and commercialization, including the following:

- the timing and progress of preclinical and clinical development activities;
- the number and scope of preclinical and clinical programs we decide to pursue;
- raising additional funds necessary to complete preclinical and clinical development of and commercialize our drug candidates;
- the progress of the development efforts of parties with whom we may enter into collaboration arrangements;

- our ability to maintain our current research and development programs and to establish new ones;
- our ability to establish new licensing or collaboration arrangements;
- the successful initiation and completion of clinical trials with safety, tolerability and efficacy profiles that are satisfactory to the U.S. Food and Drug Administration, or FDA, or any comparable foreign regulatory authority;
- the receipt and related terms of regulatory approvals from applicable regulatory authorities;
- the availability of specialty raw materials for use in production of our product candidates;
- our ability to consistently manufacture our product candidates for use in clinical trials;
- our ability to establish and operate a manufacturing facility, or secure manufacturing supply through relationships with third parties;
- our ability to obtain and maintain patents, trade secret protection and regulatory exclusivity, both in the United States and internationally;
- our ability to protect our rights in our intellectual property portfolio;
- the commercialization of our product candidates, if and when approved;
- obtaining and maintaining third-party insurance coverage and adequate reimbursement;
- the acceptance of our product candidates, if approved, by patients, the medical community and third-party payors;
- competition with other products; and
- a continued acceptable safety profile of our therapies following approval.

A change in the outcome of any of these variables with respect to the development of any of our product candidates could significantly change the costs and timing associated with the development of that product candidate. We may never succeed in obtaining regulatory approval for any of our product candidates.

General and Administrative Expenses

General and administrative expenses consist primarily of salaries and related costs, including stock-based compensation, for personnel in executive, finance and administrative functions. General and administrative expenses also include direct and allocated facility-related costs as well as professional fees for legal, patent, consulting, investor and public relations, accounting and audit services. We anticipate that our general and administrative expenses will increase in the future as we increase our headcount and infrastructure to support the expansion of our research activities and development of our product candidates. We also anticipate that we will incur increased accounting, audit, legal, regulatory, compliance and director and officer insurance costs as well as investor and public relations expenses associated with operating as a public company.

Other Income (Expense)

Change in Fair Value of Preferred Stock Warrant Liability

In connection with our 2015 loan and security agreement with Pacific Western Bank, we issued warrants to purchase Series A and Series B preferred stock. We classified these warrants as a liability on our consolidated balance sheet that we remeasured to fair value at each reporting date, and we recognized changes in the fair value of the warrant liability as a component of other income (expense) in our consolidated statements of operations and comprehensive loss. Upon the

closing of our IPO in July 2018, the preferred stock warrants became exercisable for common stock instead of preferred stock and were concurrently exercised by the holders. As a result, the fair value of the warrants was reclassified to additional paid-in capital and we no longer have a warrant liability to remeasure.

Interest Expense

Interest expense consists of interest expense on outstanding borrowings under our loan and security agreements, as well as amortization of debt discount and debt issuance costs.

Interest Income and Other Expense, Net

Interest income consists of interest earned on our invested cash balances. We expect our interest income to increase as a result of investing the cash received from the sale of Series C preferred stock in February 2018 and our IPO in July 2018.

Other income (expense) consists of miscellaneous income and expense unrelated to our core operations.

Income Taxes

Since our inception, we have not recorded any income tax benefits for the net losses we have incurred in each year or for our research and development tax credits generated, as we believe, based upon the weight of available evidence, that it is more likely than not that all of our net operating loss, or NOL, carryforwards and tax credits will not be realized. As of December 31, 2018, we had U.S. federal and state net operating loss carryforwards of $93.2 million and $93.9 million, respectively, which may be available to offset future taxable income. The federal NOLs include $37.2 million which expire at various dates through 2037 and $56.0 million which carryforward indefinitely. The state NOLs expire at various dates through 2038. As of December 31, 2018, we also had U.S. federal and state research and development tax credit carryforwards of $3.0 million and $1.1 million, respectively, which may be available to offset future tax liabilities and begin to expire in 2034 and 2031, respectively. We have recorded a full valuation allowance against our net deferred tax assets at each balance sheet date.

On December 22, 2017, the Tax Cuts and Jobs Act, or the 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 a top marginal tax rate of 35% to a flat rate of 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 federal tax rate change resulted in a reduction in the gross amount of our deferred tax assets and liabilities recorded as of December 31, 2017, and a corresponding reduction in our valuation allowance. As a result, no income tax expense or benefit was recognized as of the enactment date of the TCJA.

Results of Operations

Comparison of the Years Ended December 31, 2018 and 2017

The following table summarizes our results of operations for the years ended December 31, 2018 and 2017:

	Year Ended December 31,		
	2018	2017	Change
		(in thousands)	
Revenue	$ —	$ —	$ —
Operating expenses:			
Research and development	51,769	21,226	30,543
General and administrative	39,894	22,038	17,856
Total operating expenses	91,663	43,264	48,399
Loss from operations	(91,663)	(43,264)	(48,399)
Other income (expense):			
Change in fair value of preferred stock warrant liability	(2,187)	(785)	(1,402)
Interest expense	(464)	(309)	(155)
Interest income and other income (expense), net	5,119	511	4,608
Total other income (expense), net	2,468	(583)	3,051
Net loss	$ (89,195)	$ (43,847)	$ (45,348)

Research and Development Expenses

	Year Ended December 31,		
	2018	2017	Change
		(in thousands)	
Direct research and development expenses by program:			
RTX-134	$ 9,061	$ 809	$ 8,252
RTX-240 (formerly RTX-212)	345	—	345
Platform development, early-stage research and unallocated expenses:			
Personnel related	13,955	5,278	8,677
Stock-based compensation expense	3,787	1,756	2,031
External manufacturing and research	9,462	6,594	2,868
Laboratory supplies and research materials	8,338	4,123	4,215
Facility related and other	6,821	2,666	4,155
Total research and development expenses	$ 51,769	$ 21,226	$ 30,543

Research and development expenses were $51.8 million for the year ended December 31, 2018, compared to $21.2 million for the year ended December 31, 2017. The increase in direct costs related to our RTX-134 program of $8.3 million was primarily due to contract manufacturing costs incurred and IND-enabling activities in preparation for our planned Phase 1b clinical trial of RTX-134 in patients with phenylketonuria. The increases in personnel-related costs and stock-based compensation expense of $8.7 million and $2.0 million, respectively, were due primarily to increased headcount in our research and development function. The increase in laboratory supplies and research materials of $4.2 million was primarily due to increases in platform development, manufacturing process and scale-up and drug discovery activities. The increase in facility-related and other expenses of $4.2 million was primarily due to an increase in facilities costs resulting from entering into two leases of office and laboratory space in July 2017 and May 2018, as well as additional laboratory services to support increased headcount.

General and Administrative Expenses

	Year Ended December 31,		
	2018	2017	Change
	(in thousands)		
Personnel related	$ 6,772	$ 2,301	$ 4,471
Stock-based compensation expense	23,741	16,147	7,594
Professional and consultant fees	6,623	3,149	3,474
Facility related and other	2,758	441	2,317
Total general and administrative expenses	$ 39,894	$ 22,038	$ 17,856

General and administrative expenses for the year ended December 31, 2018 were $39.9 million, compared to $22.0 million for the year ended December 31, 2017. The increase in general and administrative expenses of $17.9 million was primarily due to an increase in stock-based compensation expense of $7.6 million. The increase in stock-based compensation expense was primarily due to the recognition of compensation expense of $7.3 million for the year ended December 31, 2018 for stock-based awards granted to new employees during the years ended December 31, 2018 and 2017 as compared to $0.3 million of compensation expense recognized in the same period in 2017, as well as the recognition of compensation expense of $2.0 million for option awards with performance-based vesting conditions that were achieved during the year ended December 31, 2018, offset by a decrease of $2.0 million in compensation expense for stock-based awards granted to the chairman of our board of directors. Personnel-related costs increased by $4.5 million as a result of an increase in headcount in our general and administrative function as we prepared for our IPO and began to operate as a public company. Professional and consultant fees increased by $3.5 million primarily due to increased patent costs as we expanded our patent portfolio, consulting fees paid to the chairman of our board of directors for his services as a consultant and increases in accounting, public relations, investor relations, audit, legal, board fees and other consulting fees incurred as we began to operate as a public company. The increase in facility related and other expenses of $2.3 million was primarily due to an increase in facilities costs resulting from entering into two leases of office and laboratory space in July 2017 and May 2018, office costs to support increased headcount, as well as additional insurance costs resulting from operating as a public company.

Change in Fair Value of Preferred Stock Warrant Liability

The change in the fair value of our preferred stock warrant liability was due to the increase in the value of our preferred stock prior to the warrant becoming a warrant for common stock upon the closing of our IPO.

Interest Expense

Interest expense was $0.5 million for the year ended December 31, 2018, compared to $0.3 million for the year ended December 31, 2017. The increase in interest expense was due to higher interest rates applicable to outstanding borrowings during the year ended December 31, 2018, as well as a loss of less than $0.1 million on the extinguishment of our 2015 loan and security agreement.

Interest Income and Other Income (Expense), Net

Interest income for the year ended December 31, 2018 was $5.1 million compared to $0.6 million in the year ended December 31, 2017. Interest income increased primarily as a result of higher invested balances due to cash proceeds received from our Series C preferred stock financing in February 2018 and our IPO in July 2018.

Other income (expense), net was not significant during the year ended December 31, 2018 or 2017.

Comparison of the Years Ended December 31, 2017 and 2016

The following table summarizes our results of operations for the years ended December 31, 2017 and 2016:

	Year Ended December 31,		
	2017	2016	Change
		(in thousands)	
Revenue	$ —	$ —	$ —
Operating expenses:			
Research and development	21,226	8,403	12,823
General and administrative	22,038	2,449	19,589
Total operating expenses	43,264	10,852	32,412
Loss from operations	(43,264)	(10,852)	(32,412)
Other income (expense):			
Change in fair value of preferred stock warrant liability	(785)	1	(786)
Interest expense	(309)	(149)	(160)
Interest income and other income (expense), net	511	(16)	527
Total other income (expense), net	(583)	(164)	(419)
Net loss	$ (43,847)	$ (11,016)	$ (32,831)

Research and Development Expenses

	Year Ended December 31,		
	2017	2016	Change
		(in thousands)	
Direct research and development expenses by program:			
RTX-134	$ 809	$ —	$ 809
Platform development, early-stage research and unallocated expenses:			
Personnel related	5,278	2,828	2,450
Stock-based compensation expense	1,756	107	1,649
External manufacturing and research	6,594	3,450	3,144
Laboratory supplies and research materials	4,123	1,160	2,963
Facility related and other	2,666	858	1,808
Total research and development expenses	$ 21,226	$ 8,403	$ 12,823

Research and development expenses were $21.2 million for the year ended December 31, 2017, compared to $8.4 million for the year ended December 31, 2016. The increase in direct costs related to our RTX-134 program of $0.8 million was primarily due to contract manufacturing costs incurred with a supplier of lentiviral vectors. The increases in personnel-related costs and stock-based compensation expense of $2.5 million and $1.6 million, respectively, were primarily due to increased headcount in our research and development function, as well as an increase in the number of awards granted and the per share fair value of such awards. The increase in external manufacturing and research costs of $3.1 million was primarily due to our efforts to improve and scale our manufacturing capabilities, preparation for clinical-scale production and an expansion of our in vivo testing to support clinical candidate selection. The increase in laboratory supplies and research materials of $3.0 million was primarily due to increases in platform development, manufacturing process and drug discovery activities, as well as an increase in the volume and cost of bioprocessing materials as we scale up our manufacturing process. The increase in facility-related and other expenses of $1.8 million was primarily due to an increase in facilities costs resulting from entering into leases of office and laboratory space in September 2016 and July 2017.

General and Administrative Expense

	Year Ended December 31,		
	2017	2016	Change
		(in thousands)	
Personnel related	$ 2,301	$ 560	$ 1,741
Stock-based compensation expense	16,147	40	16,107
Professional and consultant fees	3,149	1,465	1,684
Facility related and other	441	384	57
Total general and administrative expenses	$ 22,038	$ 2,449	$ 19,589

General and administrative expenses for the year ended December 31, 2017 were $22.0 million, compared to $2.4 million for the year ended December 31, 2016. The increase in general and administrative expenses of $19.6 million was primarily due to an increase in stock-based compensation expense of $16.1 million. The increase in stock-based compensation expense was primarily due to the recognition of compensation expense of $15.7 million for stock-based awards granted to the chairman of our board of directors during the year ended December 31, 2017. All of the stock-based awards issued to the chairman of our board of directors were for his services as a consultant and were being accounted for as non-employee stock-based awards. At the end of each reporting period prior to completion of the services, we remeasured the fair value of any unvested portion of the awards and adjusted the expense accordingly. As a result, changes in the fair value of our common stock impacted the amount of stock-based compensation expense that we recognized for these awards during the year ended December 31, 2017. The stock-based compensation expense recognized for these awards during 2017 reflects the vesting of approximately one-half of the awards. Stock-based compensation expense related to the unvested portion of the awards will be recognized over the remaining two-year service period of the awards. The remaining increase in stock-based compensation expense in 2017 was primarily due to increased headcount in our general and administrative function, as well as an increase in the number of awards granted and the per share grant-date fair value of such awards. Personnel-related costs increased by $1.7 million as a result of the increase in headcount in our general and administrative function. Professional and consultant fees increased by $1.7 million primarily due to consulting fees paid to the chairman of our board of directors for his services as a consultant, as well as increased patent costs and professional fees relating to accounting, audit and legal fees and costs associated with ongoing business activities and our preparations to operate as a public company.

Change in Fair Value of Preferred Stock Warrant Liability

The change in the fair value of our preferred stock warrant liability was $0.8 million during the year ended December 31, 2017 and was due primarily to the increase in the value of our preferred stock.

Interest Expense

Interest expense was $0.3 million for the year ended December 31, 2017, compared to $0.1 million for the year ended December 31, 2016. The increase in interest expense was due to an increase of $1.5 million in outstanding borrowings under our 2015 loan and security agreement during the year ended December 31, 2017 as well as higher interest rates applicable to outstanding borrowings during the year ended December 31, 2017.

Interest Income and Other Income (Expense), Net

Interest income for the year ended December 31, 2017 was $0.6 million due to interest earned on invested cash balances. We did not invest our cash balances during the year ended December 31, 2016.

Other expense was not significant for the years ended December 31, 2017 and 2016.

Liquidity and Capital Resources

Since our inception, we have incurred significant operating losses. We have not yet commercialized any of our product candidates and we do not expect to generate revenue from sales of any product candidates for several years, if at all. To date, we have funded our operations with proceeds from the sale of preferred stock and issuance of debt and, most

recently, with proceeds from our initial public offering, or IPO. As of December 31, 2018, we had cash, cash equivalents and investments of $404.1 million. In July 2018, we completed our IPO, pursuant to which we issued and sold 12,055,450 shares of common stock, inclusive of 1,572,450 shares pursuant to the full exercise of the underwriters' option to purchase additional shares. We received proceeds of $254.3 million, after deducting underwriting discounts and commissions and other offering costs. In December 2018, the company repaid all borrowings under its 2015 loan and security agreement and entered into a new loan and security agreement for an aggregate principal amount of $75.0 million, of which $25.0 million was drawn as of December 31, 2018.

Cash Flows

The following table summarizes our sources and uses of cash for each of the periods presented:

	Year Ended December 31,		
	2018	2017	2016
	(in thousands)		
Cash used in operating activities	$ (58,341)	$ (21,938)	$ (9,502)
Cash used in investing activities	(111,639)	(2,251)	(443)
Cash provided by financing activities	374,829	121,693	15,418
Net increase in cash, cash equivalents and restricted cash	$ 204,849	$ 97,504	$ 5,473

Operating Activities

During the year ended December 31, 2018, operating activities used $58.3 million of cash, primarily resulting from our net loss of $89.2 million, partially offset by net non-cash charges of $30.7 million, primarily consisting of stock-based compensation expense. Changes in our operating assets and liabilities for the year ended December 31, 2018 provided net cash of $0.1 million, which consisted primarily of a $9.2 million increase in accounts payable and accrued expenses and other current liabilities, offset by a $9.1 million increase in prepaid expenses and other current assets and others assets.

During the year ended December 31, 2017, operating activities used $21.9 million of cash, primarily resulting from our net loss of $43.8 million, partially offset by net non-cash charges of $19.2 million, primarily consisting of stock-based compensation expense, and net cash provided by changes in our operating assets and liabilities of $2.7 million. Net cash provided by changes in our operating assets and liabilities for the year ended December 31, 2017 consisted primarily of a $3.4 million increase in accounts payable and accrued expenses and other current liabilities, partially offset by a $0.6 million increase in prepaid expenses and other current assets.

During the year ended December 31, 2016, operating activities used $9.5 million of cash, primarily resulting from our net loss of $11.0 million, partially offset by net non-cash charges of $0.4 million and net cash provided by changes in our operating assets and liabilities of $1.1 million. Net cash provided by changes in our operating assets and liabilities for the year ended December 31, 2016 consisted primarily of a $1.2 million increase in accounts payable and accrued expenses and other current liabilities.

Changes in accounts payable, accrued expenses and other current liabilities and prepaid expenses and other assets in both periods were generally due to growth in our business, the advancement of our research programs and the timing of vendor invoicing and payments.

Investing Activities

During the year ended December 31, 2018, net cash used in investing activities was $111.6 million, consisting of purchases of investments of $161.0 million and purchases of property, plant and equipment of $15.0 million, offset by sales and maturities of investments of $64.3 million. Our purchases of property, plant and equipment primarily consisted of $8.0 million for the acquisition of and subsequent design and demolition activities associated with our recently purchased manufacturing facility in Smithfield, Rhode Island and $4.4 million for the purchase of laboratory equipment as we expanded our discovery and manufacturing activities.

During the years ended December 31, 2017 and 2016, net cash used in investing activities was $2.3 million and $0.4 million, respectively, due to purchases of property and equipment. The purchases of property and equipment during the year ended December 31, 2017 related to equipment purchases as we expanded our discovery and manufacturing activities.

Financing Activities

During the year ended December 31, 2018, net cash provided by financing activities of $374.8 million consisted primarily of $257.9 million of proceeds from our IPO in July 2018, $101.0 million of proceeds from the issuance of preferred stock in February 2018, and $25.0 million of proceeds received from borrowings under a loan and security agreement entered in December 2018, net of financing costs paid in 2018. We used cash of $5.5 million to repay outstanding borrowings under our 2015 loan and security agreement.

During the year ended December 31, 2017, net cash provided by financing activities was $121.7 million, consisting primarily of proceeds from the issuance of preferred stock of $120.1 million and borrowings of $1.5 million under our 2015 loan and security agreement.

During the year ended December 31, 2016, net cash provided by financing activities was $15.4 million, consisting primarily of proceeds from the issuance of preferred stock of $11.4 million and borrowings of $4.0 million under our 2015 loan and security agreement.

Loan and Security Agreements

In November 2018, we entered into a loan and security agreement, as amended, or the 2015 Credit Facility, with Pacific Western Bank under which we borrowed an aggregate of $5.5 million. In December 2018, we repaid all borrowings under the 2015 Credit Facility and terminated it. The aggregate principal amount of the loan outstanding at the time of repayment was $5.5 million and we did not incur any penalties as a result of the repayment. We recognized a loss on the extinguishment of the 2015 Credit Facility of less than $0.1 million related to the unamortized debt discount at the time of repayment. The loss on extinguishment was recorded as additional interest expense.

In December 2018, or the Closing Date, we entered into a loan and security agreement, or the Loan Agreement, with Solar Capital Ltd. as collateral agent for the lenders party thereto for an aggregate principal amount of $75.0 million, or the 2018 Credit Facility. The aggregate principal amount will be funded in three tranches of term loans of $25.0 million each. On the Closing Date, we made an initial draw of $25.0 million. The second tranche will be available to us through June 30, 2019, subject to certain conditions including the satisfaction of certain financial covenants. The third tranche will be available to us through June 30, 2020, subject to certain conditions including the Food and Drug Administration's acceptance of at least one of our investigational new drug applications and the satisfaction of certain financial covenants.

Interest on the outstanding loan balance will accrue at a rate of the one-month U.S. LIBOR rate plus 5.50%. Monthly principal payments will commence 36 months after the Closing Date and will be amortized over the following 24 months. The term loans are subject to a prepayment fee of 1.00% in the first year, 0.50% in the second year and 0.25% in the third year. In conjunction with 2018 Credit Facility, the company incurred issuance costs of $0.8 million.

The Loan Agreement contains financial covenants that require us to maintain either a certain minimum cash balance or a minimum market capitalization threshold. We were in compliance with all such covenants as of December 31, 2018. The Loan Agreement contains customary representations, warranties and covenants and also includes customary events of default, including payment defaults, breaches of covenants, change of control and a material adverse change default. Upon the occurrence of an event of default, a default interest rate of an additional 4.00% per annum may be applied to the outstanding loan balances, and the lenders may declare all outstanding obligations immediately due and payable. Borrowings under the Loan Agreement are collateralized by substantially all of the company's assets, other than its intellectual property.

Funding Requirements

We expect our expenses to increase substantially in connection with our ongoing activities, particularly as we advance the preclinical activities and clinical trials for our product candidates in development. In addition, upon the closing of this offering, we expect to incur additional costs associated with operating as a public company. The timing and amount of our operating and capital expenditures will depend largely on:

- the timing and progress of preclinical and clinical development activities;
- the commencement, enrollment or results of the planned clinical trials of our product candidates or any future clinical trials we may conduct, or changes in the development status of our product candidates;
- the timing and outcome of regulatory review of our product candidates;
- our decision to initiate a clinical trial, not to initiate a clinical trial or to terminate an existing clinical trial;
- changes in laws or regulations applicable to our product candidates, including but not limited to clinical trial requirements for approvals;
- developments concerning our CMOs;
- our ability to obtain materials to produce adequate product supply for any approved product or inability to do so at acceptable prices;
- the costs and timing associated with the renovation, customization and operation of our planned multi-suite manufacturing facility that we purchased in July 2018;
- our ability to establish collaborations if needed;
- the costs and timing of future commercialization activities, including product manufacturing, marketing, sales and distribution, for any of our product candidates for which we obtain marketing approval;
- the legal patent costs involved in prosecuting patent applications and enforcing patent claims and other intellectual property claims;
- additions or departures of key scientific or management personnel;
- unanticipated serious safety concerns related to the use of our product candidates; and
- the terms and timing of any collaboration, license or other arrangement, including the terms and timing of any milestone payments thereunder.

We believe that our existing cash, cash equivalents and investments, will enable us to fund our operating expenses, capital expenditure requirements, including the renovation and customization of the manufacturing facility we purchased in July 2018, and debt service payments into 2021. We have based this estimate on assumptions that may prove to be wrong, and we could utilize our available capital resources sooner than we expect.

Until such time, if ever, as we can generate substantial product revenue, we expect to finance our operations through a combination of equity offerings, debt financings, collaborations, strategic alliances and marketing, distribution or licensing arrangements. To the extent that we raise additional capital through the sale of equity or convertible debt securities, investors' ownership interest will be diluted, and the terms of these securities may include liquidation or other preferences that adversely affect investors' rights as a common stockholder. Debt financing and preferred equity financing, if available, may involve agreements that include covenants limiting or restricting our ability to take specific actions, such as incurring additional debt, making acquisitions or capital expenditures or declaring dividends. If we raise

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

Contractual Obligations and Commitments

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

	Payments Due by Period				
	Total	Less Than 1 Year	1 to 3 Years	4 to 5 Years	More Than 5 Years
	(in thousands)				
Operating lease commitments(1)	$ 61,388	$ 5,458	$ 14,309	$ 13,844	$ 27,777
Debt obligations(2)	34,092	2,005	4,010	27,089	988
Total	$ 95,480	$ 7,463	$ 18,319	$ 40,933	$ 28,765

(1) Amounts in table reflect payments due for our leases of office and laboratory space in Cambridge, Massachusetts under four operating lease agreements that expire in February 2019, February 2019, September 2021 and July 2028.

(2) Amounts in table reflect the contractually required principal and interest payments payable under the 2018 Credit Facility. For purposes of this table, the interest due under the 2018 Credit Facility was calculated using an assumed interest rate of 8.02% per annum, which was the interest rate in effect as of December 31, 2018.

We enter into contracts in the normal course of business with CROs, CMOs and other third parties for preclinical research studies, clinical trials and testing and manufacturing services. These contracts do not contain minimum purchase commitments and are cancelable by us upon prior written notice. Payments due upon cancellation consist only of payments for services provided or expenses incurred, including noncancelable obligations of our service providers, up to the date of cancellation. These payments are not included in the table above as the amount and timing of such payments are not known.

We have also entered into a license agreement with the Whitehead Institute for Biomedical Research ("WIBR"), as amended, under which the company has been granted an exclusive, sublicensable, nontransferable license under certain patent families related to the development of the company's red cell therapeutics (the "WIBR License").

We are obligated to pay to WIBR low single-digit royalties based on annual net sales by us, our affiliates and our sublicensees of licensed products and licensed services that are covered by a valid claim of the licensed patent rights at the time and in the country of sale. Based on the progress the company makes in the advancement of products covered by the licensed patent rights, the company is required to make aggregate milestone payments of up to $1.6 million upon the achievement of specified preclinical, clinical and regulatory milestones. In addition, the company is required to pay to WIBR a percentage of the non-royalty payments that it receives from sublicensees of the patent rights licensed by WIBR. This percentage varies from low single-digit to low double-digit percentages and will be based upon the clinical stage of the product that is the subject of the sublicense. Royalties shall be paid by the company on a licensed product-by-licensed product and country-by-country basis, beginning on the first commercial sale of such licensed product in such country until expiration of the last valid patent claim covering such licensed product in such country.

The company has the right to terminate the WIBR License in its entirety, on a patent-by-patent or country-by-country basis, at will upon three months' notice to WIBR. WIBR may terminate the agreement upon breach of contract or in the event of the company's bankruptcy, liquidation, insolvency or cessation of business related to the license. For additional information, see "Business—Licenses."

Critical Accounting Policies and Significant Judgments and Estimates

Our consolidated financial statements are prepared in accordance with generally accepted accounting principles in the United States, or GAAP. The preparation of our consolidated financial statements and related disclosures requires us to make estimates, assumptions and judgments that affect the reported amounts of assets, liabilities, revenue, costs and expenses, and related disclosures. We base our estimates on historical experience, known trends and events and various other factors that we believe are reasonable under the circumstances, the results of which form the basis for making judgments about the carrying values of assets and liabilities that are not readily apparent from other sources. We evaluate our estimates and assumptions on an ongoing basis. Our actual results may differ from these estimates under different assumptions or conditions.

While our significant accounting policies are described in more detail in Note 2 to our consolidated financial statements, we believe that the following accounting policies are those most critical to the judgments and estimates used in the preparation of our financial statements.

Accrued Research and Development Expenses

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

- vendors in connection with preclinical development activities;
- CMOs in connection with process development and scale-up activities and the production of preclinical and clinical trial materials; and
- CROs in connection with clinical trials.

We base the expense recorded related to contract research and manufacturing on our estimates of the services received and efforts expended pursuant to quotes and contracts with multiple CMOs and CROs that supply materials and conduct services. The financial terms of these agreements are subject to negotiation, vary from contract to contract and may result in uneven payment flows. There may be instances in which payments made to our vendors will exceed the level of services provided and result in a prepayment of the expense. In accruing service fees, we estimate the time period over which services will be performed and the level of effort to be expended in each period. If the actual timing of the performance of services or the level of effort varies from the estimate, we adjust the accrual or prepaid expense accordingly. Although we do not expect our estimates to be materially different from amounts actually incurred, our understanding of the status and timing of services performed relative to the actual status and timing of services performed may vary and may result in reporting amounts that are too high or too low in any particular period. To date, there have not been any material adjustments to our prior estimates of accrued research and development expenses.

Stock-based Compensation

We measure stock-based awards with service-based and performance-based vesting conditions granted to employees and directors and, commencing January 1, 2018, to non-employees based on their fair value on the date of the grant using the Black-Scholes option-pricing model for options or the difference between the purchase price per share of the award, if any, and the fair value of our common stock for restricted common stock awards. Compensation expense for those awards is recognized over the requisite service period, which is generally the vesting period of the respective award. We use the straight-line method to record the expense of awards with service-based vesting conditions. We use the

graded-vesting method to record the expense of awards with both service-based and performance-based vesting conditions, commencing when achievement of the performance condition becomes probable.

Prior to the adoption of ASU 2018-07, which was effective January 1, 2018, we measured the fair value of stock-based awards granted to non-employees on the date that the related service is complete, which was generally the vesting date of the award. Prior to the service completion date, compensation expense was recognized over the period during which services were rendered by such non-employees. At the end of each financial reporting period prior to the service completion date, the fair value of these awards was remeasured using the then-current fair value of our common stock and updated assumption inputs in the Black-Scholes option-pricing model for options or the difference between the purchase price per share of the award, if any, and the then-current fair value of our common stock for restricted common stock awards.

In addition, for restricted stock awards under which restricted common stock was purchased by the holder with a promissory note treated as a nonrecourse note for accounting purposes, we measured the fair value of the award using the Black-Scholes option-pricing model.

The Black-Scholes option-pricing model uses as inputs the fair value of our common stock and assumptions we make for the volatility of our common stock, the expected term of our common stock options, the risk-free interest rate for a period that approximates the expected term of our common stock options, and our expected dividend yield.

We measure the fair value of stock-based awards with market-based vesting conditions on the date of grant using a Monte Carlo simulation model. When service-based vesting conditions also exist, we recognize stock-based compensation expense using the graded-vesting method over the longer of the derived service period from the market condition or the required service period. In accordance with accounting guidance for awards with market conditions, the stock-based compensation expense will be recognized over the appropriate period regardless of whether the award achieves the market condition and will only be adjusted to the extent the service condition is not met. When an award contains a market-based vesting condition and a performance-based vesting condition where both must be achieved to earn the award, we recognize stock-based compensation expense over the longer of the derived service period from the market condition or the period estimated for the performance-based vesting condition to be achieved. We begin recording stock based compensation expense for this type of award when the achievement of the performance-based vesting condition becomes probable regardless of whether the market condition has been achieved.

Off-Balance Sheet Arrangements

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

Recently Issued Accounting Pronouncements

A description of recently issued accounting pronouncements that may potentially impact our financial position, results of operations or cash flows are disclosed in Note 2 to our consolidated financial statements.

Emerging Growth Company Status

The Jumpstart Our Business Startups Act of 2012 permits an “emerging growth company” such as us to take advantage of an extended transition period to comply with new or revised accounting standards applicable to public companies until those standards would otherwise apply to private companies. We have elected not to “opt out” of such extended transition period, which means that when a standard is issued or revised and it has different application dates for public or private companies, we will adopt the new or revised standard at the time private companies adopt the new or revised standard and will do so until such time that we either (i) irrevocably elect to “opt out” of such extended transition period or (ii) no longer qualify as an emerging growth company. While we have not made such an irrevocable election, we have not delayed the adoption of any applicable accounting standards.

Item 7A. Quantitative and Qualitative Disclosure about Market Risk

As of December 31, 2018, we had cash, cash equivalents and investment of $404.1 million, which consisted of cash, U.S. government money market funds, U.S government treasury bills, U.S. government agency bonds and U.S. government treasury notes. Interest income is sensitive to changes in the general level of interest rates; however, due to the nature of these investments, an immediate 10% change in interest rates would not have a material effect on the fair market value of our investment portfolio.

As of December 31, 2018 we had $25.0 million of borrowings outstanding under the 2018 Credit Facility. Outstanding borrowings under the 2018 Credit Facility accrue at a rate of the one-month U.S. LIBOR rate plus 5.50%. An immediate 10% change in the one-month U.S. LIBOR rate would not have a material impact on our debt-related obligations, financial position or results of operations.

We are not currently exposed to significant market risk related to changes in foreign currency exchange rates; however, we have contracted with and may continue to contract with foreign vendors that are located in Europe and Australia. Our operations may be subject to fluctuations in foreign currency exchange rates in the future.

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. Consolidated Financial Statements and Supplementary Data

RUBIUS THERAPEUTICS, INC.

Index to Consolidated Financial Statements

Report of Independent Registered Public Accounting Firm

To the Board of Directors and Stockholders of Rubius Therapeutics, Inc.

Opinion on the Financial Statements

We have audited the accompanying consolidated balance sheets of Rubius Therapeutics, Inc. and its subsidiaries (the "Company") as of December 31, 2018 and 2017, and the related consolidated statements of operations and comprehensive loss, of convertible preferred stock and stockholders' equity (deficit) and of cash flows for each of the three years in the period ended December 31, 2018, including the related notes (collectively referred to as the "consolidated financial statements"). In our opinion, the consolidated financial statements present fairly, in all material respects, the financial position of the Company as of December 31, 2018 and 2017, and the results of its operations and its cash flows for each of the three years in the period ended December 31, 2018 in conformity with accounting principles generally accepted in the United States of America.

Change in Accounting Principle

As discussed in Note 2 to the consolidated financial statements, the Company changed the manner in which it accounts for share-based compensation issued to non-employees in 2018.

Basis for Opinion

These consolidated financial statements are the responsibility of the Company's management. Our responsibility is to express an opinion on the Company's 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 of these consolidated financial statements in accordance with the standards of the PCAOB. Those standards require that we plan and perform the audit to obtain reasonable assurance about whether the consolidated financial statements are free of material misstatement, whether due to error or fraud.

Our audits included performing procedures to assess the risks of material misstatement of the consolidated financial statements, whether due to error or fraud, and performing procedures that respond to those risks. Such procedures included examining, on a test basis, evidence regarding the amounts and disclosures in the consolidated financial statements. Our audits also included evaluating the accounting principles used and significant estimates made by management, as well as evaluating the overall presentation of the consolidated financial statements. We believe that our audits provide a reasonable basis for our opinion.

/s/ PricewaterhouseCoopers LLP

Boston, Massachusetts
March 28, 2019

We have served as the Company's auditor since 2016.

RUBIUS THERAPEUTICS, INC.
CONSOLIDATED BALANCE SHEETS
(In thousands, except share and per share amounts)

	December 31,	
	2018	2017
Assets		
Current assets:		
Cash and cash equivalents	$ 307,064	$ 104,288
Investments	96,987	—
Prepaid expenses and other current assets	9,737	700
Restricted cash	622	—
Total current assets	414,410	104,988
Property, plant and equipment, net	62,796	2,415
Restricted cash	1,735	284
Other assets	168	—
Total assets	$ 479,109	$ 107,687
Liabilities, Convertible Preferred Stock and Stockholders' Equity (Deficit)		
Current liabilities:		
Accounts payable	$ 7,886	$ 2,033
Accrued expenses and other current liabilities	12,118	2,986
Current portion of long-term debt	—	2,139
Total current liabilities	20,004	7,158
Long-term debt, net of discount and current portion	24,347	3,302
Deferred rent	143	158
Preferred stock warrant liability	—	866
Liability for early exercise of stock options and restricted stock	166	100
Lease liability, net of current portion	41,441	—
Total liabilities	86,101	11,584
Commitments and contingencies (Note 12)		
Convertible preferred stock (Series A, B and C), $0.001 par value; no shares and 44,070,808 shares authorized at December 31, 2018 and 2017, respectively; no shares and 43,933,006 shares issued and outstanding at December 31, 2018 and 2017, respectively	—	139,790
Stockholders' equity (deficit):		
Preferred stock, $0.001 par value; 10,000,000 shares and no shares authorized at December 31, 2018 and 2017, respectively; no shares issued or outstanding at December 31, 2018 and 2017	—	—
Common stock, $0.001 par value; 150,000,000 and 65,000,000 shares authorized at December 31, 2018 and 2017, respectively; 79,234,853 and 14,977,317 shares issued and outstanding at December 31, 2018 and 2017, respectively	79	15
Additional paid-in capital	543,040	17,277
Accumulated other comprehensive loss	(29)	—
Accumulated deficit	(150,082)	(60,979)
Total stockholders' equity (deficit)	393,008	(43,687)
Total liabilities, convertible preferred stock and stockholders' equity (deficit)	$ 479,109	$ 107,687

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

RUBIUS THERAPEUTICS, INC.
CONSOLIDATED STATEMENTS OF OPERATIONS AND COMPREHENSIVE LOSS
(In thousands, except share and per share amounts)

	Year Ended December 31,		
	2018	2017	2016
Revenue	$ —	$ —	$ —
Operating expenses:			
Research and development	51,769	21,226	8,403
General and administrative	39,894	22,038	2,449
Total operating expenses	91,663	43,264	10,852
Loss from operations	(91,663)	(43,264)	(10,852)
Other income (expense):			
Change in fair value of preferred stock warrant liability	(2,187)	(785)	1
Interest expense	(464)	(309)	(149)
Interest income and other income (expense), net	5,119	511	(16)
Total other income (expense), net	2,468	(583)	(164)
Net loss	(89,195)	(43,847)	(11,016)
Accretion of Series A redeemable convertible preferred stock to redemption value	—	(656)	(748)
Net loss attributable to common stockholders	$ (89,195)	$ (44,503)	$ (11,764)
Net loss per share attributable to common stockholders, basic and diluted	$ (2.27)	$ (5.55)	$ (1.63)
Weighted average common shares outstanding, basic and diluted	39,285,468	8,023,785	7,200,581
Comprehensive loss:			
Net loss	$ (89,195)	$ (43,847)	$ (11,016)
Other comprehensive loss:			
Unrealized losses on investments, net of tax of $0	(29)	—	—
Comprehensive loss	$ (89,224)	$ (43,847)	$ (11,016)

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

RUBIUS THERAPEUTICS, INC.
CONSOLIDATED STATEMENTS OF CONVERTIBLE PREFERRED STOCK AND STOCKHOLDERS' EQUITY (DEFICIT)
(In thousands, except share amounts)

	Convertible preferred stock		Common stock		Additional paid-in capital	Accumulated other comprehensive loss	Accumulated deficit	Total stockholders' equity (deficit)
	Shares	Amount	Shares	Amount				
Balances at December 31, 2015	10,487,329	$ 6,882	7,505,000	$ 8	$ —	$ —	$ (5,570)	$ (5,562)
Issuance of Series A redeemable convertible preferred stock, net of issuance costs of $13	19,083,333	11,437	—	—	—	—	—	—
Issuance of common stock for technology license	—	—	366,667	—	55	—	—	55
Issuance of common stock upon exercise of stock options	—	—	14,625	—	—	—	—	—
Stock-based compensation expense	—	—	—	—	147	—	—	147
Accretion of Series A redeemable convertible preferred stock to redemption value	—	748	—	—	(202)	—	(546)	(748)
Net loss	—	—	—	—	—	—	(11,016)	(11,016)
Balances at December 31, 2016	29,570,662	19,067	7,886,292	8	—	—	(17,132)	(17,124)
Issuance of Series B convertible preferred stock, net of issuance costs of $433	14,362,344	120,067	—	—	—	—	—	—
Issuance of common stock upon exercise of stock options	—	—	250,572	—	37	—	—	37
Issuance of common stock for one-time bonus payment	—	—	213,439	—	—	—	—	—
Issuance of restricted common stock upon early exercise of stock options	—	—	1,400,000	1	(1)	—	—	—
Issuance of restricted common stock	—	—	5,227,014	6	(6)	—	—	—
Stock-based compensation expense	—	—	—	—	17,903	—	—	17,903
Accretion of Series A redeemable convertible preferred stock to redemption value	—	656	—	—	(656)	—	—	(656)
Net loss	—	—	—	—	—	—	(43,847)	(43,847)
Balances at December 31, 2017	43,933,006	139,790	14,977,317	15	17,277	—	(60,979)	(43,687)
Issuance of Series C convertible preferred stock, net of issuance costs of $214	7,912,432	100,986	—	—	—	—	—	—
Conversion of preferred stock warrant to common stock warrant upon closing of initial public offering	—	—	—	—	3,053	—	—	3,053
Conversion of redeemable convertible preferred stock to common stock	(51,845,438)	(240,776)	51,845,438	52	240,724	—	—	240,776
Issuance of common stock, initial public offering, net of issuance costs of $3,548	—	—	12,055,450	12	254,306	—	—	254,318
Cashless exercise of warrants	—	—	131,273	—	—	—	—	—
Vesting of restricted common stock	—	—	—	—	180	—	—	180
Issuance of common stock upon exercise of stock options	—	—	225,375	—	64	—	—	64
Stock-based compensation expense	—	—	—	—	27,528	—	—	27,528
Cumulative effect adjustment for adoption of ASU 2018-07	—	—	—	—	(92)	—	92	—
Unrealized losses on investments	—	—	—	—	—	(29)	—	(29)
Net loss	—	—	—	—	—	—	(89,195)	(89,195)
Balances at December 31, 2018	—	$ —	79,234,853	$ 79	$ 543,040	$ (29)	$ (150,082)	$ 393,008

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

RUBIUS THERAPEUTICS, INC.
CONSOLIDATED STATEMENTS OF CASH FLOWS
(in thousands)

	Year ended December 31,		
	2018	2017	2016
Cash flows from operating activities:			
Net loss	$ (89,195)	$ (43,847)	$ (11,016)
Adjustments to reconcile net loss to net cash used in operating activities:			
Stock-based compensation expense	27,528	17,903	147
Depreciation and amortization expense	1,263	447	118
Issuance of common stock for technology license	—	—	55
Change in fair value of preferred stock warrant liability	2,187	785	(1)
Accretion of discount on investments	(329)	—	—
Loss on disposal of property and equipment	—	—	29
Non-cash interest expense	86	42	27
Changes in operating assets and liabilities:			
Prepaid expenses and other current assets	(9,037)	(647)	(36)
Other assets	(74)	—	—
Accounts payable	4,938	1,110	589
Accrued expenses and other current liabilities	4,307	2,247	618
Deferred rent	(15)	22	(32)
Net cash used in operating activities	(58,341)	(21,938)	(9,502)
Cash flows from investing activities:			
Purchases of property, plant and equipment	(14,952)	(2,251)	(443)
Purchases of investments	(160,972)	—	—
Sales and maturities of investments	64,285	—	—
Net cash used in investing activities	(111,639)	(2,251)	(443)
Cash flows from financing activities:			
Proceeds from issuance of convertible preferred stock, net of issuance costs	100,986	120,067	11,437
Proceeds from initial public offering of common stock, net of commissions and underwriting discounts	257,866	—	—
Payments of initial public offering costs	(3,548)	—	—
Proceeds from issuance of common stock upon exercise of stock options	64	37	—
Proceeds from the sale of restricted common stock	—	100	—
Proceeds from repayment of promissory note	246	—	—
Payments of debt issuance costs	(285)	(11)	(19)
Proceeds from borrowings under loan and security agreement	25,000	1,500	4,000
Payment of long-term debt	(5,500)	—	—
Net cash provided by financing activities	374,829	121,693	15,418
Net increase in cash, cash equivalents and restricted cash	204,849	97,504	5,473
Cash, cash equivalents and restricted cash at beginning of period	104,572	7,068	1,595
Cash, cash equivalents and restricted cash at end of period	$ 309,421	$ 104,572	$ 7,068
Supplemental cash flow information:			
Cash paid for interest	$ 385	$ 265	$ 115
Supplemental disclosure of non-cash investing and financing information:			
Purchases of property, plant and equipment included in accounts payable or accrued expenses	$ 1,550	$ 9	$ 266
Landlord incentives for leasehold improvements recorded as deferred rent	$ —	$ —	$ 100
Amounts capitalized under build-to-suit lease transaction	$ 45,142	$ —	$ —
Debt issuance costs included in accounts payable and accrued expenses	$ 489	$ —	$ —
Issuance of preferred stock warrant in connection with loan and security agreement	$ —	$ 14	$ —
Reclassification of warrants to additional paid-in capital	$ 3,053	$ —	$ —
Accretion of Series A redeemable convertible preferred stock to redemption value	$ —	$ 656	$ 748
Conversion of preferred stock to common stock upon closing of the initial public offering	$ 240,776	$ —	$ —

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

RUBIUS THERAPEUTICS, INC.
NOTES TO CONSOLIDATED FINANCIAL STATEMENTS

1. Nature of the Business and Basis of Presentation

Rubius Therapeutics, Inc. ("Rubius" or the "Company") is a therapeutics company focused on using its platform to develop red cell therapeutics for the treatment of patients with severe diseases. Rubius was incorporated in April 2013 as VL26, Inc. under the laws of the State of Delaware. In January 2015, the Company changed its name to Rubius Therapeutics, Inc.

The Company is subject to risks and uncertainties common to early-stage companies in the biotechnology industry, including, but not limited to, development by competitors of new technological innovations, dependence on key personnel, protection of proprietary technology, compliance with government regulations, the ability to establish clinical- and commercial-scale manufacturing processes and the ability to secure additional capital to fund operations. In addition, the Company is subject to uncertainty regarding the performance and safety of red cell therapeutics in humans. Product candidates currently under development will require significant additional research and development efforts, including extensive preclinical and clinical testing and regulatory approval prior to commercialization. These efforts require significant amounts of additional capital, adequate personnel and infrastructure and extensive compliance-reporting capabilities. Even if the Company's drug development efforts are successful, it is uncertain when, if ever, the Company will realize significant revenue from product sales.

On July 20, 2018, the Company completed its initial public offering ("IPO"), pursuant to which it issued and sold 12,055,450 shares of common stock, inclusive of 1,572,450 shares sold by the Company pursuant to the full exercise of the underwriters' option to purchase additional shares. The aggregate net proceeds received by the Company from the IPO were $254.3 million, after deducting underwriting discounts and commissions and other offering costs. Upon the closing of the IPO, all of the shares of the Company's outstanding convertible preferred stock then outstanding automatically converted into 51,845,438 shares of common stock (see Note 7).

The accompanying consolidated financial statements have been prepared on the basis of continuity of operations, realization of assets and the satisfaction of liabilities and commitments in the ordinary course of business. The Company has incurred recurring losses since inception, including net losses of $89.2 million, $43.8 million and $11.0 million for the years ended December 31, 2018, 2017 and 2016, respectively. As of December 31, 2018, the Company had an accumulated deficit of $150.1 million. The Company expects to continue to generate operating losses in the foreseeable future. As of March 28, 2019, the issuance date of the consolidated financial statements, the Company expects that its cash, cash equivalents and investments will be sufficient to fund its operating expenses and capital expenditure requirements for at least 12 months from the issuance date of the consolidated financial statements. The Company may seek additional funding through private or public equity financings, debt financings, collaborations, strategic alliances and marketing, distribution or licensing arrangements. The Company may not be able to obtain financing on acceptable terms, or at all, and the Company may not be able to enter into collaborations or other arrangements. The terms of any financing may adversely affect the holdings or the rights of the Company's stockholders. If the Company is unable to obtain funding, the Company could be forced to delay, reduce or eliminate some or all of its research and development programs, product portfolio expansion or commercialization efforts, which could adversely affect its business prospects. Although management continues to pursue these plans, there is no assurance that the Company will be successful in obtaining sufficient funding on terms acceptable to the Company to fund continuing operations, if at all.

The Company's consolidated financial statements have been prepared in conformity with accounting principles generally accepted in the United States of America ("GAAP").

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

2. Summary of Significant Accounting Policies

Use of Estimates

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

Concentrations of Credit Risk and of Significant Suppliers

Financial instruments that potentially expose the Company to concentrations of credit risk consist primarily of cash, cash equivalents, and investments. The Company's cash equivalents and investments as of December 31, 2018 consisted of U.S. government money market funds, U.S government treasury bills, U.S. government agency bonds and U.S. government treasury notes. The Company does not believe that it is subject to unusual credit risk beyond the normal credit risk associated with commercial banking relationships.

The Company relies, and expects to continue to rely, on a small number of vendors to manufacture supplies and raw materials for its development programs. These programs could be adversely affected by a significant interruption in these manufacturing services or the availability of raw materials.

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 an equity financing, these costs are recorded in stockholders' equity (deficit) as a reduction of additional paid-in capital generated as a result of the offering. Should the in-process equity financing be abandoned, the deferred offering costs will be expensed immediately as a charge to operating expenses in the statements of operations and comprehensive loss.

Deferred Financing Costs

The Company capitalizes certain legal and other third-party fees that are directly associated with obtaining access to capital under credit facilities. Deferred financing costs incurred in connection with obtaining access to capital are recorded in other assets and are amortized over the term of the credit facility. Deferred financing costs related to a recognized debt liability are recorded as a reduction of the carrying amount of the debt liability and amortized to interest expense using the effective interest method over the repayment term.

Cash Equivalents

The Company considers all highly liquid investments with original maturities of three months or less at the date of purchase to be cash equivalents.

Restricted Cash

As of December 31, 2018 and 2017, the Company maintained restricted cash totaling $1.8 million and $0.3 million, respectively, held in the form of cash-secured letters of credit for the benefit of the landlords of its leased properties. As of December 31, 2018, the Company also maintained restricted cash of $0.5 million to collateralize its corporate credit card. The Company classified $1.7 million and $0.3 million of the restricted cash as a non-current asset in its

consolidated balance sheet as of December 31, 2018 and 2017, respectively, and classified $0.6 million of the restricted cash as a current asset in its consolidated balance sheet as of December 31, 2018.

Property, Plant and Equipment

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

	Estimated useful life
Laboratory and office equipment	5 years
Computers and software	3 years
Furniture and fixtures	7 years
Building	30 years
Leasehold improvements	Shorter of life of lease or 10 years

Costs for capital assets not yet placed into service are capitalized as construction-in-progress and depreciated once placed into service. Interest costs incurred during the construction of major capital projects are capitalized until the underlying asset is ready for its intended use, at which point the interest costs are amortized as depreciation expense over the life of the underlying asset. Upon retirement or sale, the cost of assets disposed of and the related accumulated depreciation and amortization are removed from the accounts and any resulting gain or loss is included in loss from operations. Expenditures for repairs and maintenance are charged to expense as incurred.

Impairment of Long-Lived Assets

Long-lived assets consist of property and equipment. Long-lived assets to be held and used are tested for recoverability whenever events or changes in business circumstances indicate that the carrying amount of the assets may not be fully recoverable. Factors that the Company considers in deciding when to perform an impairment review include significant underperformance of the business in relation to expectations, significant negative industry or economic trends and significant changes or planned changes in the use of the assets. If an impairment review is performed to evaluate a long-lived asset group for recoverability, the Company compares forecasts of undiscounted cash flows expected to result from the use and eventual disposition of the long-lived asset group to its carrying value. An impairment loss would be recognized in loss from operations when estimated undiscounted future cash flows expected to result from the use of an asset group are less than its carrying amount. The impairment loss would be based on the excess of the carrying value of the impaired asset group over its fair value, determined based on discounted cash flows. The Company did not record any impairment losses on long-lived assets during the periods presented.

Fair Value Measurements

Certain assets and liabilities are carried at fair value under GAAP. Fair value is defined as the exchange price that would be received for an asset or paid to transfer a liability (an exit price) in the principal or most advantageous market for the asset or liability in an orderly transaction between market participants on the measurement date. Valuation techniques used to measure fair value must maximize the use of observable inputs and minimize the use of unobservable inputs. Financial assets and liabilities carried at fair value are to be classified and disclosed in one of the following three levels of the fair value hierarchy, of which the first two are considered observable and the last is considered unobservable:

- Level 1—Quoted prices in active markets for identical assets or liabilities.
- Level 2—Observable inputs (other than Level 1 quoted prices), such as quoted prices in active markets for similar assets or liabilities, quoted prices in markets that are not active for identical or similar assets or liabilities, or other inputs that are observable or can be corroborated by observable market data.
- Level 3—Unobservable inputs that are supported by little or no market activity and that are significant to determining the fair value of the assets or liabilities, including pricing models, discounted cash flow methodologies and similar techniques.

The Company's cash equivalents and investments determined according to the fair value hierarchy described above (see Note 3). The carrying values of the Company's accounts payable and accrued expenses approximate their fair values due to the short-term nature of these liabilities. The carrying value of the Company's long-term debt approximates its fair value due to its variable interest rate, which approximates a market interest rate.

Investments

The Company's investments are classified as available-for-sale and are carried at fair value, with the unrealized gains and losses reported as a component of accumulated other comprehensive income (loss) in stockholders' equity (deficit). Realized gains and losses and declines in value determined to be other than temporary are based on the specific identification method and are included as a component of other income (expense), net in the consolidated statements of operations and comprehensive loss. The Company classifies its investments with maturities beyond one year as short-term, based on their highly liquid nature and because such investments are available for current operations.

The Company evaluates its investments with unrealized losses for other-than-temporary impairment. When assessing investments for other-than-temporary declines in value, the Company considers such factors as, among other things, how significant the decline in value is as a percentage of the original cost, how long the market value of the investment has been less than its original cost, the Company's ability and intent to retain the investment for a period of time sufficient to allow for any anticipated recovery in fair value and market conditions in general. If any adjustment to fair value reflects a decline in the value of the investment that the Company considers to be "other than temporary," the Company reduces the investment to fair value through a charge to the statement of operations and comprehensive loss. No such adjustments were necessary during the periods presented.

Classification and Accretion of Convertible Preferred Stock

The carrying value of the Company's Series A redeemable convertible preferred stock was being accreted to its redemption value from the date of issuance of such shares through the earliest date of redemption. During the year ended December 31, 2017, the redemption rights were removed from the Series A redeemable convertible preferred stock (see Note 7), and as such, the Company no longer recorded adjustments to the carrying value of its outstanding convertible preferred stock for accretion to redemption value. The Company's Series A, Series B and Series C convertible preferred stock were classified outside of stockholders' equity (deficit) because the holders of such shares had liquidation rights in the event of a deemed liquidation that, in certain situations, were not solely within the control of the Company.

Segment Information

The Company manages its operations as a single segment for the purposes of assessing performance and making operating decisions. The Company is developing red cell therapeutics for the treatment of patients with severe diseases. All of the Company's tangible assets are held in the United States.

Research and Development Costs

Research and development costs are expensed as incurred. Research and development expenses consist of costs incurred in performing research and development activities, including salaries and bonuses, stock-based compensation, employee benefits, facilities costs, laboratory supplies, depreciation, manufacturing expenses and external costs of vendors engaged to conduct preclinical development activities and clinical trials, as well as the cost of licensing technology.

Upfront payments and milestone payments made for the licensing of technology are expensed as research and development in the period in which they are incurred. Advance payments for goods or services to be received in the future for use in research and development activities are recorded as prepaid expenses. The prepaid amounts are expensed as the related goods are delivered or the services are performed.

Research and Manufacturing Contract Costs and Accruals

The Company has entered into various research and development and manufacturing contracts. These agreements are generally cancelable, and related payments are recorded as the corresponding expenses are incurred. The Company records accruals for estimated ongoing costs. When evaluating the adequacy of the accrued liabilities, the Company analyzes progress of the research studies or clinical trials and manufacturing activities, including the phase or completion of events, invoices received and contracted costs. Significant judgments and estimates are made in determining the accrued balances at the end of any reporting period. Actual results could differ from the Company's estimates. The Company's historical accrual estimates have not been materially different from the actual costs.

Patent Costs

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

Stock-Based Compensation

The Company measures stock options with service-based vesting or performance-based vesting granted to employees, non-employees and directors based on the fair value on the date of grant using the Black-Scholes option-pricing model. The Company measures restricted common stock awards using the difference between the purchase price per share of the award, if any, and the fair value of the Company's common stock. Compensation expense for those awards is recognized over the requisite service period, which is generally the vesting period of the respective award. The Company uses the straight-line method to record the expense of awards with only service-based vesting conditions. The Company uses the graded-vesting method to record the expense of awards with both service-based and performance-based vesting conditions, commencing once achievement of the performance condition becomes probable.

Prior to the adoption of ASU 2018-07 effective January 1, 2018 discussed below, the Company measured the fair value of stock-based awards granted to non-employees on the date that the related service was complete, which was generally the vesting date of the award. Prior to the service completion date, compensation expense was recognized over the period during which services were rendered by such non-employees. At the end of each financial reporting period prior to the service completion date, the fair value of these awards was remeasured using the then-current fair value of the Company's common stock and updated assumption inputs in the Black-Scholes option-pricing model for options or the difference between the purchase price per share of the award, if any, and the then-current fair value of the Company's common stock for restricted common stock awards.

For stock-based awards with market-based vesting conditions, the Company measures the fair value on the date of grant using a Monte Carlo simulation model. When service-based vesting conditions also exist, the Company recognizes stock-based compensation expense using the graded-vesting method over the longer of the derived service period from the market condition or the required service period. In accordance with accounting guidance for awards with market conditions, the stock-based compensation expense will be recognized over the appropriate period regardless of whether the award achieves the market condition and will only be adjusted to the extent the service condition is not met. When an award contains a market-based vesting condition and a performance-based vesting condition where both must be achieved to earn the award, the Company recognizes stock-based compensation expense over the longer of the derived service period from the market condition or the period estimated for the performance-based vesting condition to be achieved. The Company begins recording stock based compensation expense for this type of award once the achievement of the performance-based vesting condition becomes probable regardless of whether the market condition has been achieved.

For restricted stock awards under which restricted common stock is purchased by the holder with a promissory note treated as a nonrecourse note for accounting purposes, the Company measures the fair value of the award using the Black-Scholes option-pricing model.

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

Comprehensive Loss

Comprehensive loss includes net loss as well as other changes in stockholders' equity (deficit) that result from transactions and economic events other than those with stockholders. For the year ended December 31, 2018, the Company's only element of other comprehensive loss was unrealized losses on marketable securities. For the years ended December 31, 2017 and 2016, there was no difference between net loss and comprehensive loss in the accompanying consolidated financial statements.

Net Income (Loss) per Share

Prior to the closing of its IPO, the Company followed the two-class method when computing net income (loss) per share, as the Company had issued shares that met the definition of participating securities. The two-class method determines net income (loss) per share for each class of common and participating securities according to dividends declared or accumulated and participation rights in undistributed earnings. The two-class method requires income available to common stockholders for the period to be allocated between common and participating securities based upon their respective rights to receive dividends as if all income for the period had been distributed. The Company's redeemable convertible preferred stock contractually entitled the holders of such shares to participate in dividends but did not contractually require the holders of such shares to participate in losses of the Company. Accordingly, in periods in which the Company reported a net loss, such losses were not allocated to such participating securities, and as a result, basic and diluted net loss per share were the same.

Subsequent to the closing of its IPO, basic net income (loss) per common share is computed by dividing the net income (loss) by the weighted average number of shares of common stock outstanding for the period. Diluted net income (loss) per common share is computed by dividing net income (loss) by the weighted average number of common shares outstanding for the period, including potential dilutive common shares assuming the dilutive effect of outstanding common stock equivalents. Accordingly, in periods in which the Company reported a net loss, dilutive common shares were not assumed to have been issued as their effect was anti-dilutive, and as a result, diluted net loss per common share was the same as basic net loss per common share.

Income Taxes

The Company accounts for income taxes using the asset and liability method, which requires the recognition of deferred tax assets and liabilities for the expected future tax consequences of events that have been recognized in the consolidated financial statements or in the Company's tax returns. Deferred tax assets and liabilities are determined on the basis of the differences between the financial statements and tax basis of assets and liabilities using enacted tax rates in effect for the year in which the differences are expected to reverse. Changes in deferred tax assets and liabilities are recorded in the provision for income taxes. The Company assesses the likelihood that its deferred tax assets will be recovered from future taxable income and, to the extent it believes, based upon the weight of available evidence, that it is more likely than not that all or a portion of the deferred tax assets will not be realized, a valuation allowance is established through a charge to income tax expense. Potential for recovery of deferred tax assets is evaluated by estimating the future taxable profits expected and considering prudent and feasible tax planning strategies.

The Company accounts for uncertainty in income taxes recognized in the consolidated financial statements by applying a two-step process to determine the amount of tax benefit to be recognized. First, the tax position must be evaluated to determine the likelihood that it will be sustained upon external examination by the taxing authorities. If the tax position is deemed more-likely-than-not to be sustained, the tax position is then assessed to determine the amount of benefit to recognize in the consolidated financial statements. The amount of the benefit that may be recognized is the largest amount that has a greater than 50% likelihood of being realized upon ultimate settlement. The provision for income taxes

includes the effects of any resulting tax reserves, or unrecognized tax benefits, that are considered appropriate as well as the related net interest and penalties.

Recently Adopted Accounting Pronouncements

In June 2018, the Financial Accounting Standards Board, (the "FASB") issued Accounting Standards Update ("ASU") No. 2018-07, *Compensation — Stock Compensation (Topic 718), Improvements to Non-Employee Share-Based Payment Accounting ("ASU 2018-07")*. This ASU is intended 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, ASU 2018-07 is effective for annual periods beginning after December 15, 2019. Early adoption was permitted for all entities but no earlier than the Company's adoption of ASU 2014-09.

The Company adopted ASU 2018-07 effective January 1, 2018 by remeasuring outstanding equity-classified awards issued to non-employees for which a measurement date had not been established as of January 1, 2018 through a cumulative-effect adjustment to accumulated deficit as of January 1, 2018. The Company has elected to estimate the expected term of options utilizing the "simplified" method for both employee and non-employee options that qualify as "plain-vanilla" options. The Company has elected to account for forfeitures for non-employee options as they occur rather than apply an estimated forfeiture rate to stock-based compensation expense.

The following table summarizes the cumulative effect to the Company's consolidated balance sheet upon the adoption of ASU 2018-07 on January 1, 2018 (in thousands):

	Balance at December 31, 2017	Adjustments	Balance at January 1, 2018
Additional paid-in capital	$ 17,277	$ (92)	$ 17,185
Accumulated deficit	$ (60,979)	$ 92	$ (60,887)

The $0.1 million adjustment is the result of the change in fair value of the unvested awards, representing awards for which a measurement date had not been established, using an expected term rather than the contractual term of the awards.

As of the adoption date of January 1, 2018, the Company had 330,917 outstanding options to non-employees for which a measurement date had not been established. As of the adoption date of January 1, 2018, the Company had 4,767,014 shares of restricted common stock held by non-employees that were being accounted for as stock options for which a measurement date had not been established (see Note 10). The weighted average fair value of these awards was $5.88 per share as of January 1, 2018. The following table presents, on a weighted average basis, the assumptions used in the Black-Scholes option-pricing model to determine the fair value of outstanding awards granted to non-employees for which a measurement date had not been established as of the adoption date of January 1, 2018:

Risk-free interest rate	2.3 %
Expected volatility	74 %
Expected dividend yield	—
Expected term (in years)	6.1
Common stock value	$ 6.28

Recently Issued Accounting Pronouncements

In February 2016, the FASB issued ASU No. 2016-02, *Leases (Topic 842)* ("ASU 2016-02"), which sets out the principles for the recognition, measurement, presentation and disclosure of leases for both parties to a contract (i.e., lessees and lessors). The new standard requires lessees to apply a dual approach, classifying leases as either finance or operating leases based on the principle of whether or not the lease is effectively a financed purchase by the lessee. This classification will determine whether lease expense is recognized based on an effective interest method or on a

straight-line basis over the term of the lease. A lessee is also required to record a right-of-use asset and a lease liability for all leases with a term of greater than 12 months regardless of their classification. Leases with a term of 12 months or less may be accounted for similar to existing guidance for operating leases today. For public entities, the guidance is effective for annual reporting periods beginning after December 15, 2018 and for interim periods within those fiscal years. Early adoption is permitted. ASU 2016-02 initially required adoption using a modified retrospective approach, under which all years presented in the financial statements would be prepared under the revised guidance. In July 2018, the FASB issued ASU No. 2018-11, *Leases (Topic 842)*, which added an optional transition method under which financial statements may be prepared under the revised guidance for the year of adoption, but not for prior years. Under the latter method, entities will recognize a cumulative catch-up adjustment to the opening balance of retained earnings in the period of adoption.

The Company has elected to adopt ASU 2016-02 effective January 1, 2019 through a cumulative-effect adjustment under ASU 2018-11. This standard provides a number of optional practical expedients in transition. The Company plans to apply the package of practical expedients to leases that commenced prior to the effective date whereby it will elect to not reassess the following: (i) whether any expired or existing contracts contain leases; (ii) the lease classification for any expired or existing leases; and (iii) initial direct costs for any existing leases. The Company expects to elect the short-term lease recognition exemption for all leases that qualify, where a right-of-use asset or lease liability will not be recognized for short term leases. The Company expects that the most significant effects of adoption will be the recognition of material new right-of-use assets and corresponding liabilities on its consolidated balance sheet related to its existing facility operating leases (see Note 12). In addition, the Company has a material lease where the Company was deemed the owner during the construction period and for which the construction was not complete as of January 1, 2019. The Company took control of the leased space during the first quarter of 2019 at which time the lease commenced. Under ASU 2016-02, as the commencement date of this material lease had not occurred, the new right-of-use assets and corresponding liabilities related to this lease would not be recognized on the consolidated balance sheet as of date of adoption, January 1, 2019, however, will be recognized upon commencement date. The Company is currently evaluating the impact that the adoption of ASU 2016-02 will have on its consolidated financial statements.

In August 2018, the FASB issued ASU No. 2018-13, *Fair Value Measurement (Topic 820): Disclosure Framework-Changes to the Disclosure Requirements for Fair Value Measurement* ("ASU 2018-13"), which modifies the disclosure requirements for fair value measurements. For all entities, this guidance is required to be adopted for annual periods beginning after December 15, 2019, including interim periods within those fiscal years. Early adoption is permitted. The Company currently is evaluating the impact the adoption of ASU 2018-13 may have on its disclosures.

3. Investments and Fair Value of Financial Assets and Liabilities

Investments by security type consisted of the following (in thousands):

	December 31, 2018			
	Amortized Cost	Gross Unrealized Gains	Gross Unrealized Losses	Fair Value
U.S. treasury notes (due within one year)	$ 79,312	$ —	$ (26)	$ 79,286
U.S. government agency bonds (due within one year)	17,704	—	(3)	17,701
	$ 97,016	$ —	$ (29)	$ 96,987

The Company did not have any investments as of December 31, 2017.

The following tables present the Company's fair value hierarchy for its assets and liabilities, which are measured at fair value on a recurring basis (in thousands):

	Fair value measurements at December 31, 2018 using:			
	Level 1	Level 2	Level 3	Total
Assets:				
Cash equivalents:				
Money market funds	$ 282,160	$ —	$ —	$ 282,160
U.S. treasury bills	—	24,904	—	24,904
Marketable securities:				
U.S. government agency bonds	—	17,701	—	17,701
U.S. treasury notes	—	79,286	—	79,286
	$ 282,160	$ 121,891	$ —	$ 404,051

	Fair value measurements at December 31, 2017 using:			
	Level 1	Level 2	Level 3	Total
Assets:				
Cash equivalents:				
Money market funds	$ 104,288	$ —	$ —	$ 104,288
Liabilities:				
Preferred stock warrant liability	$ —	$ —	$ 866	$ 866

U.S. government money market funds were valued by the Company based on quoted market prices, which represent a Level 1 measurement within the fair value hierarchy. U.S. treasury notes and U.S. government agency bonds were valued by the Company using quoted prices in active markets for similar securities, which represent a Level 2 measurement within the fair value hierarchy. There have been no changes to the valuation methods during the year ended December 31, 2018. The Company evaluates transfers between levels at the end of each reporting period. There were no transfers between Level 1, Level 2 or Level 3 during the year ended December 31, 2018 and 2017, respectively.

The preferred stock warrant liability in the table above consisted of the fair value of warrants to purchase Series A and Series B convertible preferred stock (see Note 8) and was based on significant inputs not observable in the market, which represented a Level 3 measurement within the fair value hierarchy. The Company's valuation of the preferred stock warrants utilized the Black-Scholes option-pricing model, which incorporated assumptions and estimates to value the preferred stock warrants. The Company assessed these assumptions and estimates on a quarterly basis as additional information impacting the assumptions was obtained. Changes in the fair value of the preferred stock warrants were recognized as other income (expense) in the consolidated statements of operations and comprehensive loss. Upon the closing of the IPO, the warrants for the purchase of preferred stock automatically became warrants for the purchase of common stock and the Company reclassified the carrying value of the warrants from a non-current liability to additional paid-in capital in its consolidated balance sheet.

The following table provides a roll-forward of the aggregate fair values of the Company's preferred stock warrants for which fair value was determined by Level 3 inputs (in thousands):

	Preferred stock warrant liability
Fair value at December 31, 2016	$ 67
Issuance of warrants to purchase shares of Series B convertible preferred stock	14
Change in fair value	785
Fair value at December 31, 2017	866
Change in fair value through the exercise date	2,187
Reclassification to additional paid-in capital in connection with IPO	(3,053)
Fair value at December 31, 2018	$ —

4. Property, Plant and Equipment, net

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

	December 31,	
	2018	2017
Laboratory equipment	$ 7,122	$ 2,751
Land	1,300	—
Leasehold improvements	117	117
Computer equipment	276	57
Construction-in-progress	55,828	74
	64,643	2,999
Less: Accumulated depreciation and amortization	(1,847)	(584)
	$ 62,796	$ 2,415

Manufacturing Facility

On July 31, 2018, the Company completed its purchase of a 135,000 square foot manufacturing facility located in Smithfield, Rhode Island for a purchase price of $8.0 million. In August 2018, the Company began renovations to customize this facility to manufacture clinical supply of its product candidates. Of the total purchase price, $1.3 million was allocated to the value of land acquired based on the value of comparable assets, and $6.7 million was allocated to construction in progress, as the building was not ready for its intended use. During the year ended December 31, 2018, the Company capitalized approximately $2.1 million in construction-in-progress for design and demolition costs related to the renovation project.

Construction-in-progress, as of December 31, 2018, also included $45.1 million capitalized in connection with the Company's build-to-suit lease accounting (see Note 12), $1.0 million for the Company's share of the costs of construction-in-progress for leasehold improvements related to the Company's January 2018 lease for office and laboratory space in Cambridge, Massachusetts and $0.9 million of lab equipment received but not yet placed into service.

Depreciation and amortization expense was $1.3 million, $0.4 million and $0.1 million for the years ended December 31, 2018, 2017 and 2016, respectively.

5. Accrued Expenses and Other Current Liabilities

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

	December 31,	
	2018	2017
Accrued employee compensation and benefits	$ 3,377	$ 1,339
Accrued external research and development expenses	2,252	1,230
Accrued lease liability, current portion	4,502	—
Other	1,987	417
	$ 12,118	$ 2,986

6. Debt

Long-term debt consisted of the following (in thousands):

	December 31,	
	2018	2017
Principal amount of long-term debt	$ 25,000	$ 5,500
Less: Current portion of long-term debt	—	(2,139)
Long-term debt, net of current portion	25,000	3,361
Debt discount	(653)	(59)
Long-term debt, net of discount and current portion	$ 24,347	$ 3,302

2015 Credit Facility

The Company was party to a loan and security agreement, as amended (the "2015 Credit Facility"), under which the Company had borrowed an aggregate of $5.5 million. Until May 2018, borrowings under the 2015 Credit Facility bore interest at an annual rate equal to the bank's prime rate plus 1.25%, subject to a floor of 4.5%, and were repayable in monthly interest-only payments through May 2018 and in equal monthly payments of principal plus accrued interest from June 2018 until the maturity date in November 2019.

In May 2018, the Company further amended the 2015 Credit Facility to modify the interest rate and extend the interest-only payment period and the maturity date. Subsequent to this amendment, outstanding borrowings under the 2015 Credit Facility bear interest at an annual rate equal to the bank's prime rate plus 0.75%, subject to a floor of 5.5%, and were repayable in monthly interest-only payments through May 2019 and in equal monthly payments of principal plus accrued interest from June 2019 until the maturity date in November 2020.

The May 2018 amendment to the 2015 Credit Facility was accounted for as a debt modification, rather than a debt extinguishment, based on a comparison of the present value of the cash flows under the terms of the debt immediately before and after the amendment, which resulted in a change of less than 10%. As a result, issuance costs paid to the lender in connection with the amendment were recorded as a reduction of the carrying amount of the debt liability and were not significant. Unamortized issuance costs as of the date of the modification were amortized to interest expense using the effective interest method over the revised repayment term. Issuance costs paid to third parties were recorded as expense and were not significant.

Borrowings under the 2015 Credit Facility were collateralized by substantially all of the Company's personal property, other than its intellectual property. There were no financial covenants associated with the 2015 Credit Facility; however, the Company was subject to certain affirmative and negative covenants restricting the Company's activities, including limitations on dispositions, mergers or acquisitions; encumbering its intellectual property; incurring indebtedness or liens; paying dividends; making certain investments; and engaging in certain other business transactions. The obligations under the 2015 Credit Facility were subject to acceleration upon the occurrence of specified events of default, including a material adverse change in the Company's business, operations or financial or other condition.

In December 2018, the Company repaid all borrowings under the 2015 Credit Facility. The aggregate principal amount of the loan outstanding at the time of repayment was $5.5 million and the Company did not incur any penalties as a result of the repayment. The Company recognized a loss on the extinguishment of the 2015 Credit Facility of less than $0.1 million related to the unamortized debt discount at the time of repayment. The loss on extinguishment was recorded as additional interest expense.

2018 Credit Facility

On December 21, 2018 (the "Closing Date"), the Company entered into a loan and security agreement (the "Loan Agreement") with Solar Capital Ltd. as collateral agent for the lenders party thereto for an aggregate principal amount of $75.0 million. The aggregate principal amount will be funded in three tranches of term loans of $25.0 million each. On the Closing Date, the Company made an initial borrowing of $25.0 million. The second tranche will be available to the

Company through June 30, 2019, subject to certain conditions including the satisfaction of certain financial covenants. The third tranche will be available to the Company through June 30, 2020, subject to certain conditions including the Food and Drug Administration's acceptance of at least one of the Company's investigational new drug applications and the satisfaction of certain financial covenants.

Interest on the outstanding loan balance will accrue at a rate of the one-month U.S. LIBOR rate plus 5.50%. Monthly principal payments will commence 36 months after the Closing Date and will be amortized over the following 24 months. Certain backend fees are due to the lender at the time of final repayment based on the total funded term loans. The Company accrues the backend fees that will be due at final repayment to outstanding debt by charges to interest expense over the term of the loans using the effective-interest method. The term loans are subject to a prepayment fee of 1.00% in the first year, 0.50% in the second year and 0.25% in the third year. In conjunction with 2018 Credit Facility, the Company incurred issuance costs of $0.8 million.

The Loan Agreement contains financial covenants that require the Company to maintain either a certain minimum cash balance or a minimum market capitalization threshold. The Company was in compliance with all such covenants as of December 31, 2018. The Loan Agreement contains customary representations, warranties and covenants and also includes customary events of default, including payment defaults, breaches of covenants, change of control and a material adverse change default. Upon the occurrence of an event of default, a default interest rate of an additional 4.00% per annum may be applied to the outstanding loan balances, and the lenders may declare all outstanding obligations immediately due and payable. Borrowings under the Loan Agreement are collateralized by substantially all of the Company's assets, other than its intellectual property.

As of December 31, 2018, the estimated future principal payments due were as follows (in thousands):

Year ending December 31,	
2019	$ —
2020	—
2021	—
2022	12,500
Thereafter	12,500
	$ 25,000

7. Convertible Preferred Stock

The Company had issued Series A redeemable convertible preferred stock (the "Series A Preferred Stock"), Series B convertible preferred stock (the "Series B Preferred Stock") and Series C convertible preferred stock (the "Series C Preferred Stock"). The Series A Preferred Stock, the Series B Preferred Stock and the Series C Preferred Stock are referred to collectively as the "Preferred Stock". Upon issuance of the Series A Preferred Stock, the holders of such shares were entitled to receive cumulative dividends of 8.0% per year, compounding annually, and such shares were redeemable at the option of the holder after five years from issuance date of the Series A Preferred Stock. In connection with the issuance and sale of Series B Preferred Stock in June 2017, the holders of Series A Preferred Stock agreed to remove the cumulative dividend rights and redemption features of the Series A Preferred Stock. The change to the terms of the Series A Preferred Stock was accounted for as a modification, rather than an extinguishment, of the Series A Preferred Stock based on a comparison of the fair value of the stock immediately before and after the change in terms, which resulted in a fair value change of less than 10%. This modification did not have any impact on the Company's consolidated financial statements. For periods after the June 2017 date of the modification of the Series A Preferred Stock, the Company no longer accreted the carrying value of the Series A Preferred Stock to redemption value as such shares were no longer redeemable.

In June 2017, the Company issued and sold 14,362,344 shares of Series B Preferred Stock at a price of $8.39 per share for gross proceeds of $120.5 million. The Company incurred issuance costs in connection with the Series B Preferred Stock of $0.4 million.

In February 2018, the Company issued and sold 7,912,432 shares of Series C Preferred Stock at a price of $12.79 per share for gross proceeds of $101.2 million. The Company incurred issuance costs in connection with the Series C Preferred Stock of $0.2 million.

Upon issuance of each class of Preferred Stock, the Company assessed the embedded conversion and liquidation features of the shares and determined that such features did not require the Company to separately account for these features. The Company also concluded that no beneficial conversion feature existed on the issuance date of each class of Preferred Stock.

As of December 31, 2017, Preferred Stock consisted of the following (in thousands, except share amounts):

	December 31, 2017				
	Preferred stock authorized	Preferred stock issued and outstanding	Carrying value	Liquidation preference	Common stock issuable upon conversion
Series A Preferred Stock	29,703,995	29,570,662	$ 19,723	$ 17,742	29,570,662
Series B Preferred Stock	14,366,813	14,362,344	120,067	120,500	14,362,344
	44,070,808	43,933,006	$139,790	$138,242	43,933,006

Upon the closing of the IPO in July 2018, all 51,845,438 shares of the Company's outstanding convertible preferred stock automatically converted into shares of common stock and, therefore, there was no outstanding Preferred Stock at December 31, 2018.

8. Warrants to Purchase Convertible Preferred Stock

During 2015, the Company issued warrants to purchase up to 133,333 shares of Series A Preferred Stock in connection with the 2015 Credit Facility (see Note 6). The warrants were exercisable at a price of $0.60 per share and had a contractual term of ten years from issuance. The fair value of the warrants on the issuance date of $0.1 million was recorded as a deferred financing cost and as preferred stock warrant liability.

In May 2017, the Company issued warrants to purchase up to 2,234 shares of Series B Preferred Stock in connection with an amendment to the 2015 Credit Facility (see Note 6). The warrants were exercisable at a price of $8.39 per share and had a contractual term of ten years from issuance. The fair value of the warrants on the issuance date of less than $0.1 million was recorded as a debt discount and as a preferred stock warrant liability.

The Company remeasured the fair value of the liability for these preferred stock warrants at each reporting date and recorded any adjustments as other income (expense). The warrants outstanding at each reporting date were remeasured using the Black-Scholes option-pricing model (see Note 3), and the resulting change in fair value was recorded in other income (expense) in the Company's consolidated statements of operations and comprehensive loss. For the years ended December 31, 2018, 2017 and 2016, the Company recorded other expense of $2.2 million, other expense of $0.8 million and other income of less than $0.1 million, respectively, to reflect the change in fair value of these preferred stock warrants.

Upon the closing of the IPO in July 2018, the Company's outstanding warrants to purchase Preferred Stock automatically became warrants to purchase an aggregate of 135,567 shares of common stock. In July 2018, the holders of such warrants completed a cashless exercise of the warrants, resulting in the Company's issuance of 131,273 shares of common stock, whereby 4,294 shares of common stock were withheld by the Company to pay for the exercise price of the warrants.

9. Equity

Each share of common stock entitles the holder to one vote on all matters submitted to a vote of the Company's stockholders. Common stockholders are not entitled to receive dividends, unless declared by the board of directors.

In February 2018, the Company increased the number of authorized shares of common stock from 65,000,000 shares to 75,000,000 shares. In April 2018, the Company increased the number of authorized shares of common stock from 75,000,000 shares to 78,800,000 shares. In June 2018, the Company increased the number of authorized shares of common stock from 78,800,000 shares to 79,000,000 shares.

On July 20 2018, the Company filed a restated certificate of incorporation in the State of Delaware, which, among other things, restated the number of shares of all classes of stock that the Company has authority to issue to 160,000,000 shares, consisting of (i) 150,000,000 shares of common stock, $0.001 par value per share, and (ii) 10,000,000 shares of preferred stock, $0.001 par value per share. The shares of preferred stock are undesignated.

Also on July 20, 2018, the Company completed its initial public offering ("IPO"), pursuant to which it issued and sold 12,055,450 shares of common stock, inclusive of 1,572,450 shares sold by the Company pursuant to the full exercise of the underwriters' option to purchase additional shares. The aggregate net proceeds received by the Company from the IPO were $254.3 million, after deducting underwriting discounts and commissions and other offering costs. Upon the closing of the IPO, all of the shares of the Company's outstanding convertible preferred stock then outstanding automatically converted into 51,845,438 shares of common stock (see Note 7).

10. Stock-Based Compensation

2014 Stock Incentive Plan

The Company's 2014 Stock Incentive Plan (the "2014 Plan") provided for the Company to sell or issue incentive stock options or nonqualified stock options, restricted stock, restricted stock units and other equity awards to employees, directors and consultants of the Company. The 2014 Plan was administered by the board of directors or, at the discretion of the board of directors, by a committee of the board of directors. The exercise prices, vesting and other restrictions were determined at the discretion of the board of directors, or its committee if so delegated.

Stock options granted under the 2014 Plan with service-based vesting conditions generally vested over three or four years and expired after ten years. The 2014 Plan allowed for the early exercise of unvested stock options, subject to certain restrictions, including the ability of the Company to repurchase such options upon an option holder's termination of employment with the Company if such options had not yet vested. Restricted stock granted under the 2014 Plan with service-based vesting conditions generally vested over three or four years.

The exercise price for stock options granted was not less than the fair value of common shares as determined by the board of directors as of the date of grant. The Company's board of directors valued the Company's common stock, taking into consideration its most recently available valuation of common stock performed by third parties as well as additional factors which may have changed since the date of the most recent contemporaneous valuation through the date of grant. Stock options were only granted under the 2014 Plan during the period that the Company was privately held.

The total number of shares of common stock that could have been issued under the 2014 Plan was 19,152,328 shares, of which 47,447 shares remained available for future issuance prior to the effectiveness of the Company's 2018 Stock Option and Incentive Plan (the "2018 Plan"). Upon effectiveness of the 2018 Plan in July 2018, the remaining shares available under the 2014 Plan ceased to be available for issuance and no future issuances will be made under the 2014 Plan. The shares of common stock underlying outstanding awards under the 2014 Plan that are forfeited, cancelled, held back upon exercise or settlement of an award to satisfy the exercise price or tax withholding, reacquired by the Company prior to vesting, satisfied without the issuance of stock, expire or are otherwise terminated (other than by exercise) will be added to the shares of common stock available for issuance under the 2018 Plan.

2018 Equity Incentive Plan

On July 6, 2018, the Company's board of directors adopted, and its stockholders approved, the 2018 Plan, which became effective on July 16, 2018. The 2018 Plan provides for the grant of incentive stock options, non-qualified options, stock appreciation rights, restricted stock awards, restricted stock units and other stock-based awards. The number of shares initially reserved for issuance under the 2018 Plan is 5,708,931, which shall be cumulatively increased on January 1,

2019 and each January 1 thereafter by 4% of the number of shares of the Company's common stock outstanding on the immediately preceding December 31 or such lesser number of shares determined by the Company's board of directors or compensation committee of the board of directors. The shares of common stock underlying any awards that are forfeited, cancelled, held back upon exercise or settlement of an award to satisfy the exercise price or tax withholding, reacquired by the Company prior to vesting, satisfied without the issuance of stock, expire or are otherwise terminated (other than by exercise) under the 2018 Plan and the 2014 Plan will be added back to the shares of common stock available for issuance under the 2018 Plan. As of December 31, 2018, 2,335,217 shares remained available for issuance under the 2018 Plan. The number of authorized shares reserved for issuance under the 2018 Plan was increased by 2,377,045 shares effective as of January 1, 2019.

2018 Employee Stock Purchase Plan

On July 6, 2018, the Company's board of directors adopted and its stockholders approved the 2018 Employee Stock Purchase Plan (the "ESPP"), which became effective on July 16, 2018. A total of 951,488 shares of common stock were reserved for issuance under this plan. In addition, the number of shares of common stock that may be issued under the ESPP will automatically increase on January 1, 2019, and each January 1 thereafter through January 1, 2028, by the least of (i) 951,488 shares of common stock, (ii) 1% of the number of shares of the Company's common stock outstanding on the immediately preceding December 31 or (iii) such lesser number of shares as determined by the administrator of the Company's ESPP. As of December 31, 2018, all 951,488 shares remained available for issuance under the 2018 ESPP. The number of authorized shares reserved for issuance under the ESPP was increased by 792,348 shares effective as of January 1, 2019.

Stock Option Valuation

Service-Based and Performance-Based Stock Options

The fair value of stock option grants with service-based and performance-based vesting conditions is estimated using the Black-Scholes option-pricing model. The Company estimates expected volatility based on the historical volatility of publicly traded peer companies. The Company expects to continue to do so until such time as it has adequate historical data regarding the volatility of its traded stock price following our July 2018 IPO. For options with service-based vesting conditions, the expected term of the Company's stock options has been determined utilizing the "simplified" method for awards that qualify as "plain-vanilla" options. For periods prior to the adoption of ASU 2018-07 on January 1, 2018, the expected term of stock options granted to non-employees was equal to the contractual term of the option award. Upon the adoption of ASU 2018-07 on January 1, 2018, the expected term of stock options granted to non-employees has been determined utilizing the "simplified" method for awards that qualify as "plain-vanilla" options. The risk-free interest rate is determined by reference to the U.S. Treasury yield curve in effect at the time of grant of the award for time periods approximately equal to the expected term of the award. Expected dividend yield is based on the fact that the Company has never paid cash dividends and does not expect to pay any cash dividends in the foreseeable future.

The following table presents, on a weighted average basis, the assumptions used in the Black-Scholes option-pricing model to determine the fair value of stock-based awards granted to employees, directors, and, in 2018, non-employees:

	Year ended December 31,		
	2018	2017	2016
Risk-free interest rate	2.71 %	2.05 %	1.81 %
Expected volatility	74.0 %	75.6 %	77.2 %
Expected dividend yield	—	—	—
Expected term (in years)	6.21	6.39	6.25

The following table presents the assumptions used in the Black-Scholes option-pricing model to determine the fair value of stock awards granted to non-employees, prior to the adoption of ASU 2018-07:

	Year ended December 31,	
	2017	2016
Risk-free interest rate	2.02% - 2.31%	2.35% - 2.45%
Expected volatility	74% - 85%	81% - 85%
Expected dividend yield	—	—
Expected term (in years)	6 - 10	8 - 10
Fair value of common stock	$0.19 - $6.28	$0.18 - $0.19

The following table summarizes the Company's service-based and performance-based option activity since December 31, 2017:

	Number of shares	Weighted average exercise price	Weighted average contractual term	Aggregate intrinsic value
			(in years)	(in thousands)
Outstanding as of December 31, 2017	4,661,635	$ 1.29	8.64	$ 23,264
Granted	10,405,323	12.12		
Exercised	(225,375)	0.29		
Forfeited	(56,813)	1.44		
Outstanding as of December 31, 2018	14,784,770	$ 8.93	8.89	$ 126,367
Vested and expected to vest as of December 31, 2018	14,784,770	$ 8.93	8.89	$ 126,367
Options exercisable as of December 31, 2018	2,622,981	$ 1.74	7.59	$ 37,726

The aggregate intrinsic value of stock options is calculated as the difference between the exercise price of the stock options and the fair value of the Company's common stock for those stock options that had exercise prices lower than the fair value of the Company's common stock. The aggregate intrinsic value of stock options exercised during the years ended December 31, 2018, 2017 and 2016 was $3.7 million, $3.7 million and less than $0.1 million, respectively.

The weighted average grant-date fair value of stock options granted during the years ended December 31, 2018, 2017 and 2016 was $8.71 per share, $2.74 per share and $0.12 per share, respectively.

In April 2017, an executive officer early exercised an option to purchase 1,400,000 shares of common stock, at an exercise price of $0.18 per share, for cash proceeds of $0.1 million and a promissory note for $0.2 million (see Note 14). The employee received shares of restricted common stock upon such exercise. The unvested shares of restricted common stock issued upon exercise are subject to the Company's repurchase right at the lesser of the original exercise price per share or the fair value of such shares on the repurchase date. The $0.1 million of cash proceeds from the early exercise of this stock option was recorded as a liability in the Company's consolidated balance sheet and will be reclassified to stockholders' equity (deficit) as the shares vest and the Company's repurchase rights related to such shares lapse. The promissory note was partial-recourse, but was treated as nonrecourse for accounting purposes. As a result, (i) this early exercise of common stock with a promissory note continued to be accounted for as an outstanding stock option and (ii) no receivable for amounts due under the promissory note was recorded on the Company's consolidated balance sheet. Stock-based compensation expense related to this award is being recognized over the requisite service period of the award based on the grant-date fair value of the award, which was determined using the Black-Scholes option-pricing model. On June 21, 2018, the principal balance of $0.2 million and all interest that had accrued thereon, totaling less than $0.1 million, was repaid in full by the executive officer and the promissory note was terminated (see Note 14). The portion of the repayment that was associated with vested shares for which the Company's repurchase obligations had lapsed was recorded to stockholders' equity (deficit) and the remaining amount was recorded as a liability in the consolidated balance sheet and will be recorded to stockholders' equity (deficit) as the shares vest and the Company's repurchase rights related to such shares lapse.

Market-Based Stock Options

The fair value of stock option grants with market-based vesting conditions is estimated using a Monte Carlo simulation model.

In October 2018, the Company granted to an executive officer an option to purchase 164,400 shares of common stock ("Option A") at an exercise price of $16.43 per share, vesting upon the achievement of a specified thirty-day average closing price of its common stock and the satisfaction of service-based vesting conditions, and an option to purchase 193,400 shares of common stock ("Option B") at an exercise price of $16.43 per share, vesting upon the achievement of a specified thirty-day average closing price of its common stock and the achievement of certain other performance-based vesting conditions. The Company used a Monte Carlo simulation model to estimate the grant-date fair value of the awards. Assumptions and estimates utilized in the model include the risk-free interest rate, dividend yield, expected stock volatility based on a combination of the Company's historical stock volatility since its July 2018 IPO and the historical volatility of a publicly traded set of peer companies and the estimated period to achievement of the market condition. Stock-based compensation expense for Option A is being recognized using the graded-vesting method over the longer of the derived service period from the market condition or the explicit service period required to be completed for each vesting trenche. Stock-based compensation expense for Option B will be recognized when the achievement of the performance-based vesting conditions become probable regardless of whether the market condition has been achieved. The aggregate grant date fair value of these options was $4.3 million. During the year ended December 31, 2018, the Company recorded stock-based compensation expense on Option A of $0.2 million and no stock-based compensation expense on Option B, as the performance-based vesting conditions have not yet been determined to be probable.

The following table presents, on a weighted average basis, the assumptions used in the Monte Carlo simulation model to determine the fair value of stock-based awards granted to employees:

	Year ended December 31,		
	2018	2017	2016
Risk-free interest rate	3.15 %	— %	— %
Expected volatility	69.0 %	— %	— %
Expected dividend yield	—	—	—
Derived service period (in years)	2.30	—	—

The weighted average grant-date fair value of stock options with market-based vesting conditions granted during the year ended December 31, 2018 was $11.88 per share. During the year ended December 31, 2018, none of the outstanding stock awards with market-based vesting conditions were exercised, forfeited or vested and they had no intrinsic value at December 31, 2018.

Restricted Common Stock

The Company has granted restricted common stock with service-based vesting conditions. Shares of unvested restricted common stock may not be sold or transferred by the holder. These restrictions lapse according to the time-based vesting conditions of each award. The following table summarizes the Company's restricted common stock award activity since December 31, 2017:

	Shares	Weighted average grant-date fair value
Unvested restricted common stock as of December 31, 2017	5,227,014	$ 0.514
Issued	—	—
Vested	(3,667,613)	0.519
Forfeited	—	—
Unvested restricted common stock as of December 31, 2018	1,559,401	$ 0.502

In the table above, the number of shares of unvested restricted common stock outstanding as of December 31, 2018 and December 31, 2017 excludes 670,834 shares and 1,050,000 shares, respectively, of restricted common stock that remained unvested as of those dates related to the early exercise of a stock option during the year ended December 31, 2017 in exchange for 1,400,000 shares of restricted common stock. As of December 31, 2018, shares of unvested restricted common stock totaled 2,230,235 shares, consisting of 1,559,401 shares from unvested restricted common stock awards and 670,834 shares from the early exercise of a stock option.

The aggregate intrinsic value of restricted stock awards is calculated as the positive difference between the prices paid, if any, of the restricted stock awards and the fair value of the Company's common stock. The aggregate intrinsic value of restricted stock awards that vested during the years ended December 31 2018, 2017 and 2016 was $34.0 million, $0.9 million and $0.1 million, respectively.

In April 2017, the Company issued 460,000 shares of restricted common stock, at a price of $0.19 per share, to an executive officer in exchange for a promissory note in the principal amount of $0.1 million. The promissory note was partial-recourse, but was treated as nonrecourse for accounting purposes and, as such, (i) this purchase of common stock with a promissory note was accounted for as if it were a stock option grant and (ii) no receivable for amounts due under the promissory note was recorded on the Company's consolidated balance sheet. Stock-based compensation expense related to this award is being recognized over the requisite service period of the award based on the grant-date fair value of the award, which was determined using the Black-Scholes option-pricing model. On June 21, 2018, the principal balance of $0.1 million and all interest that had accrued thereon, totaling less than $0.1 million, was repaid in full by the executive officer and the promissory note was terminated (see Note 14).

In January 2017 and May 2017, the Company issued 3,667,014 shares and 1,100,000 shares, respectively, of restricted common stock at prices of $0.19 per share and $1.65 per share, respectively, to the chairman of the Company's board of directors in exchange for two promissory notes totaling $2.5 million. The promissory notes are partial-recourse, but were treated as nonrecourse for accounting purposes and, as such, (i) each of these purchases of common stock with a promissory note was accounted for as if it were a stock option grant and (ii) no receivable for amounts due under the promissory note was recorded on the Company's consolidated balance sheet. All of the stock-based awards issued to the chairman of the Company's board of directors were issued for his services as a consultant and prior to the adoption of ASU 2018-07, which was effective January 1, 2018, were being accounted for as non-employee stock-based awards. As a result, stock-based compensation expense related to the awards was being recognized over the requisite service period of the award based on the remeasured fair value of the award at each reporting period until the award vested, which was determined using the Black-Scholes option-pricing model. Upon the adoption of ASU 2018-07, the Company valued the remaining unvested options issued to non-employees as of January 1, 2018 and is recognizing stock-based compensation over the remaining vesting period. Effective January 1, 2018, the Company no longer remeasures the fair value of options granted to non-employees at each reporting period end (see Note 2). On June 21, 2018, the aggregate principal balance of both promissory notes of $2.5 million and all interest that had accrued thereon, totaling $0.1 million, was forgiven by the Company and the promissory notes were terminated (see Note 14). The forgiveness of these promissory notes by the Company was treated as an option modification and resulted in the recognition of incremental stock-based compensation expense of $1.5 million during the year ended December 31, 2018, which represents the change in the fair value of the award on the modification date. The aggregate amount of stock-based compensation expense related to these restricted stock awards recognized during the year ended December 31, 2018 was $7.3 million. Stock-based compensation expense related to these awards will continue to be recognized over the requisite service period of the awards.

Stock-Based Compensation

The Company recorded stock-based compensation expense in the following expense categories of its consolidated statements of operations and comprehensive loss (in thousands):

	Year ended December 31,		
	2018	2017	2016
Research and development expenses	$ 3,787	$ 1,756	$ 107
General and administrative expenses	23,741	16,147	40
	$ 27,528	$ 17,903	$ 147

In October 2017, the Company issued 213,439 shares of common stock to the Company's chairman of its board of directors as payment of a one-time bonus that was payable, at his election, in cash or shares of common stock. The shares were issued out of the 2014 Plan. In connection with this issuance, the Company recorded $1.0 million of stock-based compensation expense, equal to the aggregate fair value of this common stock on the date of issuance.

Stock-based compensation expense for the year ended December 31, 2018 includes $2.2 million of stock-based compensation expense related to options for the purchase of an aggregate of 447,000 shares of common stock that have non-market, performance-based vesting conditions for which the performance condition was achieved during the year ended December 31, 2018. As of December 31, 2018, the Company has outstanding options for the purchase of an aggregate of 232,500 shares of common stock with non-market, performance-based vesting conditions whereby the achievement of the conditions has not yet been determined to be probable and, therefore, the Company has not recorded any compensation expense related to these stock options.

As of December 31, 2018, total unrecognized compensation cost related to unvested stock-based awards was $89.6 million, which is expected to be recognized over a weighted average period of 2.7 years.

11. Income Taxes

2017 U.S. Tax Reform

On December 22, 2017, the Tax Cuts and Jobs Act of 2017 (the "TCJA Act") was signed into United States law, making significant changes to the Internal Revenue Code. Changes included, but were not limited to, a corporate tax rate decrease from 35% to 21% effective for tax years beginning after December 31, 2017, the transition of U.S international taxation from a worldwide tax system to a territorial system, and a one-time transition tax on the mandatory deemed repatriation of cumulative deferred foreign earnings as of December 31, 2017. On December 22, 2017, the Securities and Exchange Commission issued Staff Accounting Bulletin No. 118 ("SAB 118"), which directed taxpayers to consider the impact of the TCJA as "provisional" when a registrant did not have the necessary information available, prepared or analyzed (including computations) in reasonable detail to complete the accounting for certain income tax effects of the TCJA. During the fourth quarter of 2018 the Company completed its accounting for the tax effects of the TCJA with no material changes.

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

All of the Company's operating losses since inception have been generated in the United States.

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

	Year ended December 31,	
	2018	2017
Federal statutory income tax rate	(21.0)%	(34.0)%
State taxes, net of federal benefit	(4.8)	(3.2)
Federal and state research and development tax credits	(2.9)	(1.4)
Stock-based compensation expense	4.5	12.8
Other	0.5	0.7
Remeasurement of deferred taxes due to the Tax Cuts and Jobs Act	—	11.1
Increase in deferred tax asset valuation allowance	23.7	14.0
Effective income tax rate	— %	— %

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

	December 31,	
	2018	2017
Deferred tax assets:		
Net operating loss carryforwards	$ 25,508	$ 10,422
Research and development tax credit carryforwards	3,824	1,241
Accrued expenses	1,139	413
Capitalized intellectual property costs	764	367
Capitalized research and development expense	120	131
Stock-based compensation expense	2,652	375
Total deferred tax assets	34,007	12,949
Deferred tax liabilities:		
Depreciation and other	(341)	(374)
Total deferred tax liabilities	(341)	(374)
Valuation allowance	(33,666)	(12,575)
Net deferred tax assets	$ —	$ —

As of December 31, 2018, the Company had U.S. federal and state net operating loss ("NOL") carryforwards of $93.2 million and $93.9 million, respectively, which may be available to offset future taxable income. The federal NOLs include $37.2 million which expire at various dates through 2037 and $56.0 million which carryforward indefinitely. The state NOLs expire at various dates through 2038. As of December 31, 2018, the Company also had U.S. federal and state research and development tax credit carryforwards of $3.0 million and $1.1 million, respectively, which may be available to offset future tax liabilities and begin to expire in 2034 and 2031, respectively. During the year ended December 31, 2018, deferred tax assets, before valuation allowance, increased by approximately $21.1 million mainly due to the operating loss incurred by the Company during that period.

Utilization of the U.S. federal and state net operating loss carryforwards and research and development tax credit carryforwards may be subject to a substantial annual limitation under Sections 382 and 383 of the Internal Revenue Code of 1986, and corresponding provisions of state law, due to ownership changes that have occurred previously or that could occur in the future. These ownership changes may limit the amount of carryforwards that can be utilized annually to offset future taxable income or tax liabilities. In general, an ownership change, as defined by Section 382, results from transactions increasing the ownership of certain stockholders or public groups in the stock of a corporation by more than 50% over a three-year period. The Company has not conducted a study to assess whether a change of control has occurred or whether there have been multiple changes of control since inception due to the significant complexity and cost associated with such a study. If the Company has experienced a change of control, as defined by Section 382, at any time since inception, utilization of the net operating loss carryforwards or research and development tax credit carryforwards would be subject to an annual limitation under Section 382, which is determined by first multiplying the value of the Company's stock at the time of the ownership change by the applicable long-term tax-exempt rate, and then could be subject to additional adjustments, as required. Any limitation may result in expiration of a portion of the net

operating loss carryforwards or research and development tax credit carryforwards before utilization. Further, until a study is completed by the Company and any limitation is known, no amounts are being presented as an uncertain tax position.

The Company has evaluated the positive and negative evidence bearing upon its ability to realize the deferred tax assets. Management has considered the Company's history of cumulative net losses incurred since inception and its lack of commercialization of any products or generation of any revenue from product sales since inception and has concluded that it is more likely than not that the Company will not realize the benefits of the deferred tax assets. Accordingly, a full valuation allowance has been established against the net deferred tax assets as of December 31, 2018 and 2017. Management reevaluates the positive and negative evidence at each reporting period.

Changes in the valuation allowance for deferred tax assets during the years ended December 31, 2018 and 2017 related primarily to the increase in net operating loss carryforwards and research and development tax credit carryforwards in 2018 and 2017, and the impact of the TCJA in 2017, and were as follows (in thousands):

	Year ended December 31,	
	2018	2017
Valuation allowance as of beginning of year	$ 12,575	$ 6,454
Decreases recorded as benefit to income tax provision	—	(4,887)
Increases recorded to income tax provision	21,091	11,008
Valuation allowance as of end of year	$ 33,666	$ 12,575

As of December 31, 2018 and 2017, the Company had not recorded any amounts for unrecognized tax benefits. The Company's policy is to record interest and penalties related to income taxes as part of its income tax provision. As of December 31, 2018 and 2017, the Company had no accrued interest or penalties related to uncertain tax positions and no amounts had been recognized in the Company's consolidated statements of operations and comprehensive loss. The Company files income tax returns in the U.S. and Massachusetts, as prescribed by the tax laws of the jurisdictions in which it operates. In the normal course of business, the Company is subject to examination by federal and state jurisdictions, where applicable. There are currently no pending tax examinations. The Company is open to future tax examination under statute from 2015 to the present; however, carryforward attributes that were generated prior to January 1, 2015 may still be adjusted upon examination by federal, state or local tax authorities if they either have been or will be used in a future period.

12. Commitments and Contingencies

Operating Leases

The Company leases its office and laboratory facilities in Cambridge, Massachusetts under three noncancelable operating leases that expire in December 2018, February 2019 and September 2021. The Company continued to occupy the facility covered by the lease expiring in December 2018 until February 2019 in accordance with the holdover provisions in the lease. The lease agreements include lease incentives, payment escalations and rent holidays, which are accrued or deferred as appropriate such that rent expense for each lease is recognized on a straight-line basis over the terms of occupancy. Rent expense for the years ended December 31, 2018, 2017 and 2016 was $2.4 million, $1.0 million and $0.4 million, respectively.

Future minimum lease payments under operating leases as of December 31, 2018 are as follows (in thousands):

Year ended December 31,	
2019	$ 956
2020	713
2021	547
	$ 2,216

Build-To-Suit Lease

In January 2018, the Company entered into a lease for office and laboratory space in Cambridge, Massachusetts (the "Initial Space"). The lease term commenced on January 28, 2019 and expires eight years from the commencement date. The Company is entitled to one five-year option to extend. The initial annual base rent is approximately $3.8 million, and such amount will increase during the initial term by 3% annually on the anniversary of the commencement date. The Company is obligated to pay its portion of real estate taxes and costs related to the premises, including costs of operations, maintenance, repair, replacement and management of the new leased premises. In connection with the lease, the Company maintains a letter of credit for the benefit of the landlord in the amount of $0.9 million, which is secured by a cash deposit of the same amount. The lease agreement allows for a landlord-provided tenant improvement allowance of $9.9 million to be applied to the costs of the construction of the leasehold improvements, of which $0.5 million is repayable to the landlord over the term of the lease.

In November 2018, the Company amended its January 2018 lease to lease additional office and laboratory space in the same building (the "Expansion Space"). The term for the Expansion Space is expected to commence in August 2019 and expires nine years from the commencement date. The initial annual base rent for the Expansion Space is approximately $2.5 million and such amount will increase by 3% annually on the anniversary of the commencement date. The Company is obligated to pay its portion of real estate taxes and costs related to the Expansion Space, including costs of operations, maintenance, repair, replacement and property management. In connection with the lease amendment, the Company increased the letter of credit held for the benefit of the landlord by $0.6 million, which is secured by a cash deposit of the same amount. The lease amendment increased the landlord-provided tenant improvement allowance by $7.2 million.

The Company is not the legal owner of the leased space. However, in accordance with ASC 840, *Leases*, the Company is deemed to be the owner of the leased space during the construction period because of certain indemnification provisions within the lease agreement. As a result, as of December 31, 2018, the Company capitalized approximately $45.1 million (equal to the estimated fair value of its leased portion of the premises) as construction-in-progress within property, plant and equipment and recorded a corresponding build-to-suit facility lease financing obligation. As of December 31, 2018, the current portion of the lease financing obligation of $4.5 million was classified within accrued expenses and other current liabilities and the remaining $41.4 million was classified as a lease liability, net of current portion, on its consolidated balance sheet. The Company took control of the Initial Space during the first quarter of 2019 at which time the lease commenced. Upon the commencement date of the Initial Space, in the first quarter of 2019, the Company assessed and determined the accounting treatment for the asset and corresponding liability under ASC 842, *Leases*, which was adopted as of January 1, 2019 according to ASU No. 2016-02 (see Note 2).

As of December 31, 2018, minimum commitments under this lease are as follows (in thousands):

Year ending December 31,	
2019	$ 4,502
2020	6,428
2021	6,621
2022	6,820
2023	7,024
Thereafter	27,777
	$ 59,172

License Agreement with the Whitehead Institute for Biomedical Research

The Company has a license agreement with the Whitehead Institute for Biomedical Research ("WIBR"), as amended, under which the Company has been granted an exclusive, sublicensable, nontransferable license under certain patent families related to the development of the Company's red cell therapies (the "WIBR License"). The Company is obligated to pay WIBR annual license maintenance fees of less than $0.1 million, as well as patent-related costs, including legal fees and low single-digit royalties based on annual net sales of licensed products and licensed services by the Company and its sublicensees. Based on the progress the Company makes in the advancement of products covered

by the licensed patent rights, the Company is required to make aggregate milestone payments of up to $1.6 million upon the achievement of specified preclinical, clinical and regulatory milestones. In addition, the Company is required to pay to WIBR a percentage of the non-royalty payments that it receives from sublicensees of the patent rights licensed by WIBR. This percentage varies from low single-digit to low double-digit percentages and will be based upon the clinical stage of the product that is the subject of the sublicense. Royalties shall be paid by the Company on a licensed product-by-licensed product and country-by-country basis, beginning on the first commercial sale of such licensed product in such country until expiration of the last valid patent claim covering such licensed product in such country.

The Company has the right to terminate the WIBR License in its entirety, on a patent-by-patent or country-by-country basis, at will upon three months' notice to WIBR. WIBR may terminate the agreement upon breach of contract or in the event of the Company's bankruptcy, liquidation, insolvency or cessation of business related to the license.

401(k) Plan

In January 2018, the Company established a defined-contribution plan under Section 401(k) of the Internal Revenue Code (the "401(k) Plan"). The 401(k) Plan covers all employees who meet defined minimum age and service requirements and allows participants to defer a portion of their annual compensation on a pre-tax basis. The Company will make matching contributions at a rate of 50% of each employee's contribution up to a maximum employee contribution of 6% of eligible plan compensation. For the year ended December 31, 2018, the Company made matching contributions of $0.2 million.

Indemnification Agreements

In the ordinary course of business, the Company may provide indemnification of varying scope and terms to vendors, lessors, contract research organizations, business partners and other parties with respect to certain matters including, but not limited to, losses arising out of breach of such agreements or from intellectual property infringement claims made by third parties. In addition, the Company has entered into indemnification agreements with members of its board of directors and certain of its executive officers that will require the Company, among other things, to indemnify them against certain liabilities that may arise by reason of their status or service as directors or officers. The maximum potential amount of future payments the Company could be required to make under these indemnification agreements is, in many cases, unlimited. The Company has not incurred any material costs as a result of such indemnifications and is not currently aware of any indemnification claims.

Legal Proceedings

The Company is not currently party to any material legal proceedings. At each reporting date, the Company evaluates whether or not a potential loss amount or a potential range of loss is probable and reasonably estimable under the provisions of the authoritative guidance that addresses accounting for contingencies. The Company expenses as incurred the costs related to such legal proceedings.

13. Net Loss per Share

Basic and diluted net loss per share attributable to common stockholders was calculated as follows (in thousands, except share and per share amounts):

	Year ended December 31,		
	2018	2017	2016
Numerator:			
Net loss	$ (89,195)	$ (43,847)	$ (11,016)
Accretion of Series A redeemable convertible preferred stock to redemption value	—	(656)	(748)
Net loss attributable to common stockholders	$ (89,195)	$ (44,503)	$ (11,764)
Denominator:			
Weighted average common shares outstanding, basic and diluted	39,285,468	8,023,785	7,200,581
Net loss per share attributable to common stockholders, basic and diluted	$ (2.27)	$ (5.55)	$ (1.63)

Upon the issuance of Series A Preferred Stock, the holders of such shares were entitled to cumulative dividends of 8.0% per year, compounding annually. In connection with the issuance and sale of Series B Preferred Stock in June 2017, the holders of Series A Preferred Stock agreed to remove the cumulative dividend and redemption rights associated with the Series A Preferred Stock. Accordingly, during the year ended December 31, 2017, the calculation of net loss attributable to common stockholders included the accretion of Series A redeemable convertible preferred stock to redemption value.

The Company's potential dilutive securities have been excluded from the computation of diluted net loss per share as the effect would be to reduce the net loss per share. Therefore, the weighted average number of common shares outstanding used to calculate both basic and diluted net loss per share attributable to common stockholders is the same. The Company excluded the following potential common shares from the periods in the table above, presented based on amounts outstanding at each period end, from the computation of diluted net loss per share attributable to common stockholders for the periods indicated because including them would have had an anti-dilutive effect:

	Year ended December 31,		
	2018	2017	2016
Convertible preferred stock (as converted to common stock)	—	43,933,006	29,570,662
Warrants to purchase convertible preferred stock (as converted to common stock)	—	135,567	133,333
Restricted common stock(1)	2,230,235	6,277,014	348,120
Stock options to purchase common stock	14,784,770	4,661,635	4,159,165
	17,015,005	55,007,222	34,211,280

(1) Includes unvested restricted stock and vested restricted stock issued for promissory notes.

14. Related Parties

In April 2013, the Company entered into a services agreement with Flagship Ventures Management, Inc. ("Flagship"), an affiliate of one of its principal stockholders, to provide general and administrative services to the Company, including certain consulting services and the provision of employee health and dental benefit plans for the Company's employees. The Company recorded general and administrative expense and made cash payments for services received under this agreement of $1.3 million, $0.9 million and $0.8 million during the years ended December 31, 2018, 2017 and 2016, respectively. As of December 31, 2018, 2017 and 2016, the Company had no amounts payable to Flagship for costs related to the services agreement.

In January 2017, the Company loaned $0.7 million to the chairman of its board of directors to purchase shares of common stock pursuant to a promissory note and a restricted stock agreement (see Note 10). In May 2017, the Company loaned $1.8 million to the chairman of its board of directors to purchase shares of common stock pursuant to a promissory note and a restricted stock agreement (see Note 10). The January 2017 promissory note provided that the unpaid principal amount of the loan bore interest at 1.97% annually, and the May 2017 promissory note provided that the unpaid principal amount of the loan bore interest at 2.04% annually. Interest was payable annually or was converted to principal and payable at the maturity date. The maturity date of the promissory notes occurred on the earliest of (i) seven years from the issuance date of the notes, (ii) 60 days following the date of termination of services of the borrower, and (iii) immediately prior to an initial filing of a registration statement by the Company. The promissory notes were partial-recourse and secured by a pledge of the shares of common stock purchased with the promissory notes. As of December 31, 2017, no amounts were due to the Company and no amounts had been received by the Company as repayment of these promissory notes. On June 21, 2018, the aggregate principal balance of both promissory notes of $2.5 million and all interest that had accrued thereon, totaling $0.1 million, was forgiven by the Company and the promissory notes were terminated.

In April 2017, the Company loaned $0.2 million to an executive officer of the Company to purchase shares of common stock pursuant to two promissory notes and two restricted stock agreements (see Note 10). The promissory notes provided that the unpaid principal amount of the loans bore interest at 2.05% annually, and interest was payable annually or was converted to principal and payable at the maturity date. The maturity date of the promissory notes occurred on the earliest of (i) seven years from the issuance date of the notes, (ii) 60 days following the date of termination of employment of the borrower, and (iii) immediately prior to an initial filing of a registration statement by the Company. The promissory notes were partial-recourse and secured by a pledge of the shares of common stock purchased with the promissory notes. As of December 31, 2017, no amounts were due to the Company and no amounts had been received by the Company as repayment of these promissory notes. On June 21, 2018, the aggregate principal balance of both promissory notes of $0.2 million and all interest that had accrued thereon, totaling less than $0.1 million, was repaid in full by the executive officer and the promissory notes were terminated.

15. Selected Quarterly Financial Data (Unaudited)

The following table contains quarterly financial information for 2018 and 2017. The information has been derived from unaudited consolidated financial statements that, in the opinion of management, include all recurring adjustments necessary for a fair statement of such information (in thousands, except per share data):

	Three Months Ended			
	March 31, 2018(1)	June 30, 2018(1)	September 30, 2018	December 31, 2018
Consolidated Statements of Operations Data:				
Revenue	$ —	$ —	$ —	$ —
Total operating expenses	14,603	20,384	27,554	29,122
Loss from operations	(14,603)	(20,384)	(27,554)	(29,122)
Net loss attributable to common stockholders	(14,411)	(21,239)	(26,362)	(27,183)
Net loss per share attributable to common stockholders, basic and diluted	$ (1.72)	$ (2.43)	$ (0.42)	$ (0.35)

	Three Months Ended			
	March 31, 2017	June 30, 2017	September 30, 2017	December 31, 2017
Consolidated Statements of Operations Data:				
Revenue	$ —	$ —	$ —	$ —
Total operating expenses	4,783	9,033	11,975	17,473
Loss from operations	(4,783)	(9,033)	(11,975)	(17,473)
Net loss attributable to common stockholders	(5,233)	(9,834)	(11,919)	(17,517)
Net loss per share attributable to common stockholders, basic and diluted	$ (0.68)	$ (1.25)	$ (1.48)	$ (2.07)

During the three months ended September 30, 2018, the Company adopted ASU 2018-07 (see Note 2) effective January 1, 2018. The Company has revised the results for the three months ended March 31, 2018 and the three months ended June 30, 2018 to reflect the adoption of ASU 2018-07.

The following tables summarize the impact of adoption to the Company's previously issued consolidated statements of operations and comprehensive loss (in thousands):

	Three Months Ended March 31, 2018		Three Months Ended June 30, 2018	
	As previously reported	As revised	As previously reported	As revised
Operating expenses:				
Research and development	$ 9,650	$ 9,506	$ 11,965	$ 11,361
General and administrative	5,797	5,097	16,279	9,023
Total operating expenses	15,447	14,603	28,244	20,384
Loss from operations	(15,447)	(14,603)	(28,244)	(20,384)
Net loss attributable to common stockholders	$ (15,255)	$ (14,411)	$ (29,099)	$ (21,239)
Net loss per share attributable to common stockholders, basic and diluted	$ (1.83)	$ (1.72)	$ (3.33)	$ (2.43)

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

None.

Item 9A. Controls and Procedures

Evaluation of Disclosure Controls and Procedures

Our management, with the participation of our Chief Executive Officer and Chief Financial Officer (our principal executive officer and principal financial officer, respectively), evaluated the effectiveness of our disclosure controls and procedures as of December 31, 2018. The term "disclosure controls and procedures," as defined in Rules 13a-15(e) and 15d-15(e) under the Exchange Act means controls and other procedures of an issuer that are designed to ensure that information required to be disclosed by an issuer in the reports that it files or submits under the Exchange Act is recorded, processed, summarized and reported, within the time periods specified in the SEC's rules and forms. Disclosure controls and procedures include, without limitation, controls and procedures designed to ensure that information required to be disclosed by an issuer in the reports that it files or submits under the Exchange Act is accumulated and communicated to the issuer's management, including its principal executive and principal financial officers, or persons performing similar functions, as appropriate to allow timely decisions regarding required disclosure.

Management recognizes that any controls and procedures, no matter how well designed and operated, can provide only reasonable assurance of achieving their objectives and management necessarily applies its judgment in evaluating the cost-benefit relationship of possible controls and procedures. Based on the evaluation of our disclosure controls and procedures as of December 31, 2018, our Chief Executive Officer and Chief Financial Officer concluded that, as of such date, our disclosure controls and procedures were effective at the reasonable assurance level.

Internal Control Over Financial Reporting

Management's Report on Internal Control Over Financial Reporting

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

Changes in Internal Control Over Financial Reporting

There were no changes in our internal control over financial reporting (as defined in Rules 13a-15(f) and 15d-15(f) under the Exchange Act) that occurred during the period covered by this report that have materially affected, or are reasonably likely to materially affect, our internal control over financial reporting.

Item 9b. Other Information

None.

PART III

Item 10. Directors, Executive Officers and Corporate Governance

Incorporated by reference from the information in our Proxy Statement for our 2019 Annual Meeting of Stockholders, which we expect to file with the SEC within 120 days of the end of the fiscal year to which this Annual Report on Form 10-K relates.

Item 11. Executive Compensation

Incorporated by reference from the information in our Proxy Statement for our 2019 Annual Meeting of Stockholders, which we expect to file with the SEC within 120 days of the end of the fiscal year to which this Annual Report on Form 10-K relates.

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

Incorporated by reference from the information in our Proxy Statement for our 2019 Annual Meeting of Stockholders, which we expect to file with the SEC within 120 days of the end of the fiscal year to which this Annual Report on Form 10-K relates.

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

Incorporated by reference from the information in our Proxy Statement for our 2019 Annual Meeting of Stockholders, which we expect to file with the SEC within 120 days of the end of the fiscal year to which this Annual Report on Form 10-K relates.

Item 14. Principal Accounting Fees and Services

Incorporated by reference from the information in our Proxy Statement for our 2019 Annual Meeting of Stockholders, which we expect to file with the SEC within 120 days of the end of the fiscal year to which this Annual Report on Form 10-K relates.

PART IV

Item 15. Exhibits and Financial Statement Schedules

(a) 1. *Financial Statements*

For a list of the financial statements included herein, see Index to the Consolidated Financial Statements on page 147 of this Annual Report on Form 10-K, incorporated into this Item by reference.

2. *Financial Statement Schedules*

Financial statement schedules have been omitted because they are either not required or not applicable or the information is included in the consolidated financial statements or the notes thereto.

3. *Exhibits*

The exhibits required by Item 601 of Regulation S-K and Item 15(b) of this Annual Report on Form 10-K are listed in the Exhibit Index below. The exhibits listed in the Exhibit Index are incorporated by reference herein.

(b) Exhibit Index

3.1	Amended and Restated Certificate of Incorporation of Rubius Therapeutics, Inc. (Incorporated by reference to Exhibit 3.1 to the Registrant's Form 8-K (File No. 001-38586) filed on July 23, 2018)
3.2	Amended and Restated Bylaws of Rubius Therapeutics, Inc. (Incorporated by reference to Exhibit 3.2 to the Registrant's Form 8-K (File No. 001-38586) filed on July 23, 2018)
4.1	Specimen Common Stock Certificate (Incorporated by reference to Exhibit 4.1 to the Registrant's Registration Statement on Form S-1, as amended (File No. 333-225840) filed on July 2, 2018)
4.2	Second Amended and Restated Investors' Rights Agreement among the Registrant and certain of its stockholders, dated February 23, 2018 (Incorporated by reference to Exhibit 4.2 to the Registrant's Registration Statement on Form S-1 (File No. 333-225840) filed on June 22, 2018)
10.1#	Amended and Restated 2014 Stock Incentive Plan, and form of award agreements thereunder ((Incorporated by reference to Exhibit 10.1 to the Registrant's Registration Statement on Form S-1 (File No. 333-225840) filed on June 22, 2018)
10.2#	2018 Stock Option and Incentive Plan, and form 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. 333-225840) filed on July 9, 2018)
10.2#	2018 Employee Stock Purchase Plan (Incorporated by reference to Exhibit 10.3 to the Registrant's Registration Statement on Form S-1, as amended (File No. 333-225840) filed on July 9, 2018)
10.3#	Senior Executive Cash Incentive Bonus Plan (Incorporated by reference to Exhibit 10.4 to the Registrant's Registration Statement on Form S-1 (File No. 333-225840) filed on June 22, 2018)
10.3#	Non-Employee Director Compensation Policy (Incorporated by reference to Exhibit 10.5 to the Registrant's Registration Statement on Form S-1, as amended (File No. 333-225840) filed on July 2, 2018)

10.4#	Employment Agreement between Rubius Therapeutics, Inc. and Pablo J. Cagnoni, M.D., dated July 2, 2018 (Incorporated by reference to Exhibit 10.6 to the Registrant's Registration Statement on Form S-1, as amended (File No. 333-225840) filed on July 9, 2018)
10.5#	Employment Agreement between Rubius Therapeutics, Inc. and Torben Straight Nissen, Ph.D., dated July 2, 2018 (Incorporated by reference to Exhibit 10.7 to the Registrant's Registration Statement on Form S-1, as amended (File No. 333-225840) filed on July 9, 2018)
10.6#	Employment Agreement between Rubius Therapeutics, Inc. and Andrew M. Oh, dated June 29, 2018 (Incorporated by reference to Exhibit 10.8 to the Registrant's Registration Statement on Form S-1, as amended (File No. 333-225840) filed on July 9, 2018)
10.7#	Employment Agreement between Rubius Therapeutics, Inc. and Christopher L. Carpenter, M.D., Ph.D., dated June 29, 2018 (Incorporated by reference to Exhibit 10.9 to the Registrant's Registration Statement on Form S-1, as amended (File No. 333-225840) filed on July 9, 2018)
10.8#	Second Amended and Restated Chairman Agreement between Rubius Therapeutics, Inc. and David R. Epstein, dated June 21, 2018 (Incorporated by reference to Exhibit 10.10 to the Registrant's Registration Statement on Form S-1 (File No. 333-225840) filed on June 22, 2018)
10.9#	Form of Indemnification Agreement between Rubius Therapeutics, Inc. and each of its directors (Incorporated by reference to Exhibit 10.14 to the Registrant's Registration Statement on Form S-1 (File No. 333-225840) filed on June 22, 2018)
10.10#	Form of Indemnification Agreement between Rubius Therapeutics, Inc. and each of its executive officers (Incorporated by reference to Exhibit 10.15 to the Registrant's Registration Statement on Form S-1 (File No. 333-225840) filed on June 22, 2018)
10.11^	Lease Agreement between Rubius Therapeutics, Inc. and ARE-MA Region No. 58 LLC, dated January 18, 2018 (Incorporated by reference to Exhibit 10.11 to the Registrant's Registration Statement on Form S-1 (File No. 333-225840) filed on June 22, 2018)
10.11.1*^^	First Amendment to Lease Agreement between Rubius Therapeutics, Inc. and ARE-MA Region No. 58 LLC, dated November 8, 2018
10.12^	Exclusive Patent License Agreement between the Registrant and the Whitehead Institute for Biomedical Research, dated January 28, 2016 and First Amendment to the Exclusive Patent License Agreement between the Registrant and the Whitehead Institute for Biomedical Research, dated December 12, 2017 (Incorporated by reference to Exhibit 10.13 to the Registrant's Registration Statement on Form S-1 (File No. 333-225840) filed on June 22, 2018)
10.12.1*^^	Second Amendment to the Exclusive Patent License Agreement between the Registrant and the Whitehead Institute for Biomedical Research, dated July 25, 2018
10.13	Purchase and Sale Agreement between Rubius Therapeutics, Inc. and Alexion Pharmaceuticals, Inc., dated July 23, 2018 (Incorporated by reference to Exhibit 10.1 to the Registrant's Form 8-K (File No. 001-38586) filed on July 25, 2018)
10.14	Loan and Security Agreement between Rubius Therapeutics, Inc. and Solar Capital Ltd. dated December 21, 2018 (Incorporated by reference to Exhibit 10.1 to the Registrant's Form 8-K (File No. 001-38586) filed on December 21, 2018)
21.1*	List of Subsidiaries of Rubius Therapeutics, Inc.

23.1*	Consent of PricewaterhouseCoopers LLP, independent registered public accounting firm
24.1*	Power of Attorney (included on signature page to this Annual Report on Form 10-K)
31.1*	Certification of Principal Executive Officer pursuant to Rule 13a-14(a) or 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) or 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 pursuant to 18 U.S.C. Section 1350, as adopted pursuant to Section 906 of the Sarbanes-Oxley Act of 2002.
32.2*†	Certification of Principal Financial Officer pursuant to 18 U.S.C. Section 1350, as adopted pursuant to Section 906 of the Sarbanes-Oxley Act of 2002.
101.INS	XBRL Instance Document.
101.SCH	XBRL Taxonomy Extension Schema Document.
101.CAL	XBRL Taxonomy 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.

\# Indicates a management contract or any compensatory plan, contract or arrangement.

^ Confidential treatment has been granted with respect to redacted portions of this exhibit. Redacted portions of this exhibit have been filed separately with the Securities and Exchange Commission.

^^ Application has been made to the Securities and Exchange Commission for confidential treatment of certain provisions. Omitted material for which confidential treatment has been requested has been filed separately with the Securities and Exchange Commission.

† This certification will not be deemed "filed" for purposes of Section 18 of the Securities Exchange Act of 1934, as amended (the "Exchange Act"), or otherwise subject to the liability of that section. Such certification will not be deemed to be incorporated by reference into any filing under the Securities Act of 1933, as amended, or the Exchange Act, except to the extent specifically incorporated by reference into such filing.

Item 16. Form 10-K Summary

The company has elected not to include summary information.

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.

RUBIUS THERAPEUTICS, INC.

By: /s/ Pablo J. Cagnoni
Pablo J. Cagnoni
Chief Executive Officer

POWER OF ATTORNEY

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

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

Signature	Title	Date
/s/ Pablo J. Cagnoni Pablo J. Cagnoni	Chief Executive Officer, Director (Principal Executive Officer)	March 28, 2019
/s/ David R. Epstein David R. Epstein	Chairman, Director	March 28, 2019
/s/ Andrew M. Oh Andrew M. Oh	Chief Financial Officer (Principal Financial Officer and Principal Accounting Officer)	March 28, 2019
Noubar B. Afeyan, Ph.D.	Director	March 28, 2019
/s/ Francis Cuss Francis Cuss, M.B., B.Chir., FRCP	Director	March 28, 2019
/s/ Robert S. Langer Robert S. Langer, Sc.D.	Director	March 28, 2019
Natalie Holles	Director	March 28, 2019
/s/ Roger Pomerantz Roger Pomerantz, M.D.	Director	March 28, 2019

Signature	Title	Date
/s/ Michael Rosenblatt Michael Rosenblatt, M.D.	Director	March 28, 2019
/s/ Catherine A. Sohn Catherine A. Sohn, Pharm.D.	Director	March 28, 2019
/s/ Jonathan R. Symonds Jonathan R. Symonds, CBE	Director	March 28, 2019

Exhibit 10.11.1

*****Text Omitted and Filed Separately with the Securities and Exchange Commission. Confidential Treatment Requested Under 17 C.F.R. §200.80(b)(4)**

FIRST AMENDMENT TO LEASE

THIS FIRST AMENDMENT TO LEASE (this "**First Amendment**") is made as of November 8, 2018, by and between **ARE-MA REGION NO. 58, LLC**, a Delaware limited liability company ("**Landlord**"), and **RUBIUS THERAPEUTICS, INC.**, a Delaware corporation ("**Tenant**").

RECITALS

A . Landlord and Tenant are now parties to that certain Lease Agreement dated as January 18, 2018 (the "**Lease**"). Pursuant to the Lease, Tenant leases certain premises consisting of approximately 48,192 rentable square feet ("**Original Premises**") in that certain to-be-constructed building to be known as 399 Binney Street, Cambridge, Massachusetts (the "**Building**"). The Original Premises are more particularly described in the Lease. Capitalized terms used herein without definition shall have the meanings defined for such terms in the Lease.

B . Landlord and Tenant desire, subject to the terms and conditions set forth below, to amend the Lease to, among other things, expand the size of the Original Premises by adding approximately 37,742 rentable square feet of space, consisting of (i) that portion of the first floor of the Building containing approximately 7,423 rentable square feet (the "**First Floor Space**"), and (ii) that portion of lower level of the Building containing approximately 30,319 rentable square feet, all as shown on **Exhibit A** attached to this First Amendment (collectively, the "**Expansion Premises**").

NOW, THEREFORE, in consideration of the foregoing Recitals, which are incorporated herein by this reference, the mutual promises and conditions contained herein, and for other good and valuable consideration, the receipt and sufficiency of which are hereby acknowledged, Landlord and Tenant hereby agree as follows:

1 . **Expansion Premises**. In addition to the Original Premises, commencing on the Expansion Premises Commencement Date (as defined below), Landlord leases to Tenant, and Tenant leases from Landlord, the Expansion Premises, subject to all of the same terms and conditions of the Lease as are applicable to the Original Premises (except as otherwise provided in this First Amendment).

2 . **Delivery of Expansion Premises**. Landlord shall use reasonable efforts to deliver the Expansion Premises to Tenant so that Tenant can occupy the Expansion Premises for the Permitted Use ("**Delivery**" or "**Deliver**") with (x) all base Building mechanical, electrical and plumbing systems serving the Expansion Premises in good operating condition and repair, and (y) free and clear of all tenants and occupants, on or before the Target Expansion Premises Commencement Date with Landlord's Work in the Expansion Premises Substantially Completed, subject to Tenant Delays and Force Majeure delays. If Landlord fails to timely Deliver the Expansion Premises, Landlord shall not be liable to Tenant for any loss or damage resulting therefrom, and the Lease and this First Amendment shall not be void or voidable. Notwithstanding anything to the contrary contained herein, if Landlord fails to Deliver the Expansion Premises to Tenant (i) on or before September 1, 2019 (as such date may be extended for Tenant Delays and Force Majeure delays) ("**Initial Expansion Abatement Date**"), Base Rent payable with respect to the Expansion Premises shall be abated 1 day for each day after the Initial Expansion Abatement Date (as such date may be extended for Tenant Delays and Force Majeure delays) that Landlord fails to Deliver the Expansion Premises to Tenant, and (ii) on or before October 1, 2019 (as such date may be extended for Tenant Delays and Force Majeure delays) ("**Second Expansion Abatement Date**"), Base Rent payable with respect to the Expansion Premises shall be abated 2 days for each day after the Second Expansion Abatement Date (as such date may be extended for Tenant Delays and Force

Majeure delays) that Landlord fails to Deliver the Expansion Premises to Tenant. If Landlord does not Deliver the Expansion Premises on or before December 1, 2019, for any reason other than Force Majeure delays and Tenant Delays, the Lease with respect to the Expansion Premises only may be terminated by Tenant by written notice to Landlord, and if so terminated by Tenant: (a) all of the provisions of this First Amendment shall terminate and be of no further force or effect, and (b) neither Landlord nor Tenant shall have any further rights, duties or obligations under the Lease with respect to the Expansion Premises, except with respect to provisions which expressly survive termination of the Lease. If Tenant does not elect to terminate the Lease with respect to the Expansion Premises on or before December 6, 2019, such right to terminate the Lease with respect to the Expansion Premises shall be waived and the Lease with respect to the Expansion Premises shall remain in full force and effect. As used herein, the terms "**Landlord's Work**," "**Tenant Delays**" and "**Substantially Completed**" shall have the meanings set forth for such terms in the work letter attached to this First Amendment as **Exhibit B** ("**Expansion Premises Work Letter**"). The Work Letter attached to the Lease as **Exhibit C** does not apply with respect to the Expansion Premises.

The "**Expansion Premises Commencement Date**" shall be the earlier to occur of: (i) the date that Landlord Delivers the Expansion Premises to Tenant, or (ii) the date that Landlord could have Delivered the Expansion Premises to Tenant but for Tenant Delays. The "**Target Expansion Premises Commencement Date**" shall be August 1, 2019.

Except as set forth in the Expansion Premises Work Letter: (i) Tenant shall accept the Expansion Premises in their condition as of the Expansion Premises Commencement Date, subject to all applicable Legal Requirements; (ii) Landlord shall have no obligation for any defects in the Expansion Premises; and (iii) Tenant's taking possession of the Expansion Premises shall be conclusive evidence that Tenant accepts the Expansion Premises and that the Expansion Premises were in good condition at the time possession was taken. Any occupancy of the Expansion Premises by Tenant before the Expansion Premises Commencement Date shall be subject to all of the terms and conditions of the Lease, including the obligation to pay Base Rent and Operating Expenses. Notwithstanding the foregoing, Base Rent and Operating Expenses shall not be payable during the period that Tenant is accessing the Expansion Premises to perform Tenant's Work (as defined in the Expansion Premises Work Letter) pursuant to Section 6 of the Expansion Premises Work Letter and not for the conduct of Tenant's business in the Expansion Premises.

Tenant agrees and acknowledges that, except as otherwise expressly set forth in this First Amendment, neither Landlord nor any agent of Landlord has made any representation or warranty with respect to the condition of all or any portion of the Expansion Premises, and/or the suitability of the Expansion Premises for the conduct of Tenant's business, and Tenant waives any implied warranty that the Expansion Premises are suitable for the Permitted Use.

3 . **Premises; Rentable Area of Premises**. Commencing on the Expansion Premises Commencement Date, the defined terms "**Premises**" and "**Rentable Area of Premises**" on page 1 of the Lease shall be deleted in their entirety and replaced with the following:

> "**Premises:** That portion of the Building containing approximately 85,934 rentable square feet, consisting of (i) the entire 3rd floor, containing approximately 47,136 rentable square feet (the "**Third Floor Space**"), (ii) a portion of the 4th floor, containing approximately 1,056 rentable square feet (the "**Fourth Floor Space**"), (iii) a portion of the first floor, containing approximately 7,423 rentable square feet (the "**First Floor Space**"), and (iv) a portion of the lower level, containing approximately 30,319 rentable square feet (the "**Lower Level Space**"), all as shown on **Exhibit A**."

"**Rentable Area of Premises:** 85,934 sq. ft."

As of the Expansion Premises Commencement Date, **Exhibit A** to the Lease shall be amended to include the Expansion Premises as shown on **Exhibit A** attached to this First Amendment.

4. **Base Rent**.

a. **Original Premises**. Tenant shall continue to pay Base Rent with respect to the Original Premises as provided for under the Lease through the Original Premises Expiration Date (as defined below).

b. **First Floor Space**. Commencing on the Expansion Premises Commencement Date, Tenant shall pay Base Rent with respect to the First Floor Space in the amount of $[***] per rentable square foot of the First Floor Space per year. On each anniversary of the Expansion Premises Commencement Date, (each, an "**Expansion Premises Adjustment Date**"), Base Rent payable with respect to the First Floor Space shall be increased by multiplying the Base Rent payable with respect to the First Floor Space immediately before such Expansion Premises Adjustment Date by [***]% and adding the resulting amount to the Base Rent payable with respect to the First Floor Space immediately prior to such Expansion Premises Adjustment Date. Base Rent adjustments for the First Floor Space for any fractional calendar month shall be prorated.

c. **Lower Level Space**. Commencing on the Expansion Premises Commencement Date, Tenant shall pay Base Rent with respect to the Lower Level Space in the amount of $[***] per rentable square foot of the Lower Level Space per year. On each Expansion Premises Adjustment Date, Base Rent payable with respect to the Lower Level Space shall be increased by multiplying the Base Rent payable with respect to the Lower Level Space immediately before such Expansion Premises Adjustment Date by [***]% and adding the resulting amount to the Base Rent payable with respect to the Lower Level Premises immediately prior to such Expansion Premises Adjustment Date. Base Rent adjustments for the Lower Level Space for any fractional calendar month shall be prorated.

d. **Additional TI Allowance**. In addition to the Tenant Improvement Allowance (as defined in the Expansion Premises Work Letter), Landlord shall, subject to the terms of the Expansion Premises Work Letter, make available to Tenant the Additional TI Allowance (as defined in the Expansion Premises Work Letter). Commencing on the Expansion Premises Commencement Date and continuing thereafter on the first day of each month through the Expansion Premises Expiration Date, Tenant shall pay the amount necessary to fully amortize the portion of the Additional TI Allowance (as defined in the Expansion Premises Work Letter) actually funded by Landlord, if any, in equal monthly payments with annual interest at a rate of 8% per annum over the Base Term, which interest shall begin to accrue on the date that Landlord first disburses such Additional TI Allowance (as defined in the Expansion Premises Work Letter) or any portion(s) thereof ("**Expansion Premises TI Rent**"). Any of the Additional TI Allowance (as defined in the Expansion Premises Work Letter) and applicable interest remaining unpaid as of the Expansion Premises Expiration Date or earlier termination of the Lease shall be paid to Landlord in a lump sum on the Expansion Premises Expiration Date or earlier termination of this Lease. Tenant, at Tenant's option, may prepay the Expansion Premises TI Rent in full at any time without penalty.

5 . **Tenant's Share**. Commencing on the Expansion Premises Commencement Date, the defined term "**Tenant's Share**" on page 1 of the Lease shall be deleted in its entirety and replaced with the following:

"**Tenant's Share:** 52.02%"

6 . **Base Term**. Commencing on the date of this First Amendment, the defined term "**Base Term**" on page 1 of the Lease shall be deleted in its entirety and replaced with the following:

"**Base Term**. Beginning on (i) the Commencement Date with respect to the Original Premises, and ending with respect to the Original Premises on the date that is 96 months from the first day of the first full month following the Commencement Date (the "**Original Premises Expiration Date**"), and (ii) the Expansion Premises Commencement Date with respect to the Expansion Premises, and ending with respect to the Expansion Premises on the date that is 108 months after the first day of the first month following the Expansion Premises Commencement Date (the "**Expansion Premises Expiration Date**").

If Tenant does not extend the Term of the Lease pursuant to Section 40 of the Lease (as amended by Section 9 of this First Amendment), then on the day immediately following the Expansion Premises Expiration Date, the definitions of "**Premises**," "**Rentable Area of Premises**" and "**Tenant's Share**" shall be adjusted to account for the expiration of the Lease with respect to the Original Premises. Otherwise, on the day immediately following the Expansion Premises Expiration Date, the definitions of **"Premises**," "**Rentable Area of Premises**" and "**Tenant's Share**" shall be adjusted to account for the expiration of the Lease with respect to the Expansion Premises.

7. **Security Deposit**. Commencing on the date of this First Amendment, the defined term "**Security Deposit**" on Page 1 of the Lease is deleted in its entirely and replaced with the following:

"**Security Deposit:** $[***]"

Landlord currently holds a Security Deposit of $[***] under the Lease. Concurrently with Tenant's delivery of a signed original of this First Amendment to Landlord, Tenant shall deliver to Landlord an amended Letter of Credit which increases the amount of the existing Letter of Credit being held by Landlord to $[***] or an additional Letter of Credit in the amount of $[***].

8 . **Parking**. Commencing on the Expansion Premises Commencement Date, subject to the terms of Section 10 of the Lease, in addition to Tenant's Parking Allocation, Tenant shall have the right, in common with other tenants of the Project to use 0.9 parking spaces per 1,000 rentable square feet of the Expansion Premises ("**Tenant's Expansion Premises Parking Allocation**") in the OKS Garage to park in those areas designated for non-reserved parking, subject in each case to Landlord's rules and regulations and Tenant's payment of the Monthly Parking Changes with respect to each parking space. Tenant has elected to use all of Tenant's Expansion Premises Parking Allocation commencing on the Expansion Premises Commencement Date. As of the date of this First Amendment, the Monthly Parking Charge is $[***] per parking space per month, plus applicable taxes.

9 . **Right to Extend Term**. Notwithstanding anything to the contrary contained in the Lease, (a) Tenant shall only have the right to exercise its Extension Right under Section 40 of the Lease with respect to the entire Premises (i.e., the Original Premises and the Expansion Premises), (b) if Tenant exercises its Extension Right pursuant to Section 40, then, (i) the Term of the Lease with respect to the Original Premises will be extended for an additional 60 months following the Original Premises Expiration Date ("**Extended Original Premises Expiration Date**"), and (ii) the Term of the Lease with respect to the Expansion Premises will be extended from the Expansion Premises Expiration Date through the Extended Original Premises Expiration Date, such that the Term of the

Lease with respect to the Original Premises and the Expansion Premises will expire concurrently. Commencing on the day immediately following the Expansion Premises Expiration Date, Tenant shall commence paying Base Rent on a per rentable square foot basis with respect to the Expansion Premises at the same Base Rent per rentable square foot that Tenant is then paying with respect to the Original Premises (as determined and as adjusted pursuant to Section 40 of the Lease). For the avoidance of doubt, Tenant shall continue to pay Base Rent as required under this First Amendment with respect to the Expansion Premises through the Expansion Premises Expiration Date.

10. **Brokers**. Landlord and Tenant each represents and warrants that it has not dealt with any broker, agent or other person (collectively, "**Broker**") in connection with the transaction reflected in this First Amendment and that no Broker brought about this transaction, other than Newmark Knight Frank. Landlord and Tenant each hereby agrees to indemnify and hold the other harmless from and against any claims by any Broker, other than Newmark Knight Frank, claiming a commission or other form of compensation by virtue of having dealt with Tenant or Landlord, as applicable, with regard to this First Amendment.

11. **OFAC**. Tenant and, to Tenant's knowledge, all beneficial owners of Tenant are currently (a) in compliance with and shall at all times during the Term of the Lease remain in compliance with the regulations of the Office of Foreign Assets Control ("**OFAC**") of the U.S. Department of Treasury and any statute, executive order, or regulation relating thereto (collectively, the "**OFAC Rules**"), (b) not listed on, and shall not during the Term of the Lease be listed on, the Specially Designated Nationals and Blocked Persons List, Foreign Sanctions Evaders List, or the Sectoral Sanctions Identification List, which are all maintained by OFAC and/or on any other similar list maintained by OFAC or other governmental authority pursuant to any authorizing statute, executive order, or regulation, and (c) not a person or entity with whom a U.S. person is prohibited from conducting business under the OFAC Rules.

12. **Miscellaneous**.

a . This First Amendment is the entire agreement between the parties with respect to the subject matter hereof and supersedes all prior and contemporaneous oral and written agreements and discussions. This First Amendment may be amended only by an agreement in writing, signed by the parties hereto.

b. This First Amendment is binding upon and shall inure to the benefit of the parties hereto, and their respective successors and assigns.

c . This First Amendment may be executed in 2 or more counterparts, each of which shall be deemed an original, but all of which together shall constitute one and the same instrument. Counterparts may be delivered via facsimile, electronic mail (including pdf or any electronic signature process complying with the U.S. federal ESIGN Act of 2000) or other transmission method and any counterpart so delivered shall be deemed to have been duly and validly delivered and be valid and effective for all purposes. Electronic signatures shall be deemed original signatures for purposes of this First Amendment and all matters related thereto, with such electronic signatures having the same legal effect as original signatures.

d. Except as amended and/or modified by this First Amendment, the Lease is hereby ratified and confirmed and all other terms of the Lease shall remain in full force and effect, unaltered and unchanged by this First Amendment. In the event of any conflict between the provisions of this First Amendment and the provisions of the Lease, the provisions of this First Amendment shall

prevail. Whether or not specifically amended by this First Amendment, all of the terms and provisions of the Lease are hereby amended to the extent necessary to give effect to the purpose and intent of this First Amendment.

[Signatures are on next page]

IN WITNESS WHEREOF, the parties hereto have executed this First Amendment as of the day and year first above written.

TENANT:

RUBIUS THERAPEUTICS, INC.,
a Delaware corporation

By: /s/ Joanne M. Protano
Print Name: Joanne M. Protano
Title: SVP Finance and Secretary

LANDLORD:

ARE-MA REGION NO. 58, LLC,
a Delaware limited liability company

BY: ALEXANDRIA REAL ESTATE EQUITIES, L.P.,
a Delaware limited partnership,
managing member

By: ARE-QRS CORP.,
a Maryland corporation,
general partner

By: /s/ Jackie Clem
Print Name: Senior Vice President
Title: RE Legal Affairs

EXHIBIT A

Expansion Premises

[***].

EXHIBIT B

Expansion Premises Work Letter

THIS **EXPANSION PREMISES WORK LETTER** (this "**Expansion Premises Work Letter**") is made by and between **ARE-MA REGION NO. 59, LLC**, a Delaware limited liability company ("**Landlord**"), and **RUBIUS THERAPEUTICS, INC.**, a Delaware corporation ("**Tenant**"), and is attached to and made a part of that certain Lease Agreement dated as of January 18, 2018, as amended by that certain First Amendment to Lease Agreement dated of even date herewith (the "**First Amendment**") (as amended, the "**Lease**"), by and between Landlord and Tenant. Any initially capitalized terms used but not defined herein shall have the meanings given them in the Lease.

1. **General Requirements**.

(a) **Tenant's Authorized Representative**. Tenant designates Joanne Protano and Torben Straight Nissen (either such individual acting alone, "**Tenant's Representative**") as the only persons authorized to act for Tenant pursuant to this Expansion Premises Work Letter. Landlord shall not be obligated to respond to or act upon any request, approval, inquiry or other communication ("**Communication**") from or on behalf of Tenant in connection with this Expansion Premises Work Letter unless such Communication is in writing from Tenant's Representative. Tenant may change either Tenant's Representative at any time upon not less than 5 business days advance written notice to Landlord. Neither Tenant nor Tenant's Representative shall be authorized to direct Landlord's contractors in the performance of Landlord's Work (as hereinafter defined).

(b) **Landlord's Authorized Representative**. Landlord designates William DePippo and Tim White (either such individual acting alone, "**Landlord's Representative**") as the only persons authorized to act for Landlord pursuant to this Expansion Premises Work Letter. Tenant shall not be obligated to respond to or act upon any request, approval, inquiry or other Communication from or on behalf of Landlord in connection with this Expansion Premises Work Letter unless such Communication is in writing from Landlord's Representative. Landlord may change either Landlord's Representative at any time upon not less than 5 business days advance written notice to Tenant. Landlord's Representative shall be the sole persons authorized to direct Landlord's contractors in the performance of Landlord's Work.

(c) **Architects, Consultants and Contractors**. Landlord and Tenant hereby acknowledge and agree that: (i) The Richmond Group shall be the general contractor (the "**General Contractor**") for the Tenant Improvements, (ii) Perkins & Will shall be the architect (the "**TI Architect**") for the Tenant Improvements, and (iii) any subcontractors for the Tenant Improvements shall be selected by Landlord, subject to Tenant's approval, which approval shall not be unreasonably withheld, conditioned or delayed. Landlord shall contract with the TI Architect and the General Contractor for the design and construction of Landlord's Work.

2. **Tenant Improvements**.

(a) **Tenant Improvements Defined**. As used herein, "**Tenant Improvements**" shall mean all improvements to the Expansion Premises of a fixed and permanent nature as shown on the TI Construction Drawings, as defined in Section 2(c) below. Other than Landlord's Work (as defined in Section 3(a)) below, Landlord shall not have any obligation whatsoever with respect to the finishing of the Expansion Premises for Tenant's use and occupancy.

(b) **Tenant's Space Plans**. Tenant shall deliver to Landlord and the TI Architect schematic drawings and outline specifications (the "**TI Design Drawings**") detailing Tenant's requirements for the Tenant Improvements within 5 business days of the date hereof. Not more than 5 business days thereafter,

Landlord shall deliver to Tenant the written objections, questions or comments of Landlord and the TI Architect with regard to the TI Design Drawings. Tenant shall cause the TI Design Drawings to be revised to address such written comments and shall resubmit said drawings to Landlord for approval within 5 business days thereafter. Such process shall continue until Landlord has approved the TI Design Drawings. It is hereby acknowledged by Landlord and Tenant that the TI Design Drawings must be completed and approved not later than January 15, 2019, in order for the Landlord's Work to be Substantially Complete by the Target Expansion Premises Commencement Date (as defined in the First Amendment).

(c) **Working Drawings**. Landlord shall cause the TI Architect to prepare and deliver to Tenant for review and comment construction plans, specifications and drawings for the Tenant Improvements ("**TI Construction Drawings**"), which TI Construction Drawings shall be prepared substantially in accordance with the TI Design Drawings. Tenant shall be solely responsible for ensuring that the TI Construction Drawings reflect Tenant's requirements for the Tenant Improvements. Tenant shall deliver its written comments on the TI Construction Drawings to Landlord not later than 10 business days after Tenant's receipt of the same; provided, however, that Tenant may not disapprove any matter that is consistent with the TI Design Drawings without submitting a Change Request. Landlord and the TI Architect shall consider all such comments in good faith and shall, within 10 business days after receipt, notify Tenant how Landlord proposes to respond to such comments, but Tenant's review rights pursuant to the foregoing sentence shall not delay the design or construction schedule for the Tenant Improvements. Any disputes in connection with such comments shall be resolved in accordance with Section 2(d) hereof. Provided that the design reflected in the TI Construction Drawings is consistent with the TI Design Drawings, Tenant shall approve in writing the TI Construction Drawings submitted by Landlord, unless Tenant submits a Change Request. Once approved by Tenant, subject to the provisions of Section 4 below, Landlord shall not materially modify the TI Construction Drawings except as may be reasonably required in connection with the issuance of the TI Permit (as defined in Section 3(b) below).

(d) **Approval and Completion**. It is hereby acknowledged by Landlord and Tenant that the TI Construction Drawings must be completed and approved not later than February 22, 2019, in order for the Landlord's Work to be Substantially Complete by the Target Expansion Premises Commencement Date. Upon any dispute regarding the design of the Tenant Improvements, which is not settled within 10 business days after notice of such dispute is delivered by one party to the other, Tenant may make the final decision regarding the design of the Tenant Improvements, provided (i) Tenant acts reasonably and such final decision is either consistent with or a compromise between Landlord's and Tenant's positions with respect to such dispute, (ii) that all costs and expenses resulting from any such decision by Tenant shall be payable out of the TI Fund (as defined in Section 5(e) below), and (iii) Tenant's decision will not affect the base Building, structural components of the Building or any Building systems. Any changes to the TI Construction Drawings following Landlord's and Tenant's approval of same requested by Tenant shall be processed as provided in Section 4 hereof.

3. **Performance of Landlord's Work**.

(a) **Definition of Landlord's Work**. As used herein, "**Landlord's Work**" shall mean the work of constructing the Tenant Improvements.

(b) **Commencement and Permitting**. Landlord shall commence construction of the Tenant Improvements upon Landlord's obtaining a building permit (the "**TI Permit**") authorizing the construction of the Tenant Improvements consistent with the TI Construction Drawings approved by Tenant as provided herein. The cost of obtaining the TI Permit shall be payable from the TI Fund. Tenant shall assist Landlord in obtaining the TI Permit. If any Governmental Authority having jurisdiction over the construction of Landlord's Work or any portion thereof shall impose terms or conditions upon the construction thereof that: (i) are inconsistent with Landlord's obligations hereunder, (ii) increase the cost of constructing Landlord's

Work, or (iii) will materially delay the construction of Landlord's Work, Landlord and Tenant shall reasonably and in good faith seek means by which to mitigate or eliminate any such adverse terms and conditions.

(c) **Completion of Landlord's Work**. Landlord shall use commercially reasonable efforts to Substantially Complete Landlord's Work by the Target Expansion Premises Commencement Date. It is hereby acknowledged by Landlord and Tenant that the permit set based on the TI Construction Drawings must be completed on or before February 22, 2019, in order for Landlord's Work to be Substantially Completed by the Target Expansion Premises Commencement Date. Landlord shall substantially complete or cause to be substantially completed Landlord's Work in a good and workmanlike manner, in accordance with the TI Permit subject, in each case, to Minor Variations and normal "punch list" items of a non-material nature that do not interfere with Tenant's use of the Expansion Premises ("**Substantial Completion**" or "**Substantially Complete**"), which punch list items shall be completed by Landlord within sixty (60) days after the date of Substantial Completion. Upon Substantial Completion of Landlord's Work, Landlord shall require the TI Architect and the General Contractor to execute and deliver, for the benefit of Tenant and Landlord, a Certificate of Substantial Completion in the form of the American Institute of Architects ("**AIA**") document G704. For purposes of this Expansion Premises Work Letter, "**Minor Variations**" shall mean any modifications reasonably required: (i) to comply with all applicable Legal Requirements and/or to obtain or to comply with any required permit (including the TI Permit); (ii) to comply with any request by Tenant for modifications to Landlord's Work; (iii) to comport with good design, engineering, and construction practices that are not material; or (iv) to make reasonable adjustments for field deviations or conditions encountered during the construction of Landlord's Work.

(d) **Selection of Materials**. Where more than one type of material or structure is indicated on the TI Construction Drawings approved by Landlord and Tenant, the option will be selected at Landlord's sole and absolute subjective discretion. As to all building materials and equipment that Landlord is obligated to supply under this Expansion Premises Work Letter, Landlord shall select the manufacturer thereof in its sole and absolute subjective discretion.

(e) **Delivery of the Expansion Premises**. When Landlord's Work is Substantially Complete, subject to the remaining terms and provisions of this Section 3(e), Tenant shall accept the Expansion Premises. Tenant's taking possession and acceptance of the Expansion Premises shall not constitute a waiver of: (i) any warranty with respect to workmanship (including installation of equipment) or material (exclusive of equipment provided directly by manufacturers), (ii) any non-compliance of Landlord's Work with applicable Legal Requirements, or (iii) any claim that Landlord's Work was not completed substantially in accordance with the TI Construction Drawings (subject to Minor Variations and such other changes as are permitted hereunder) (collectively, a "**Construction Defect**"). Tenant shall have one year after Substantial Completion within which to notify Landlord of any such Construction Defect discovered by Tenant, and Landlord shall use reasonable efforts to remedy or cause the responsible contractor to remedy any such Construction Defect within 30 days thereafter. Notwithstanding the foregoing, Landlord shall not be in default under the Lease if the applicable contractor, despite Landlord's reasonable efforts, fails to remedy such Construction Defect within such 30-day period, in which case Landlord shall continue to use reasonable efforts to cause such Construction Defect to be remedied.

Tenant shall be entitled to receive the benefit of all construction warranties and manufacturer's equipment warranties relating to equipment installed in the Expansion Premises. If requested by Tenant, Landlord shall attempt to obtain extended warranties from manufacturers and suppliers of such equipment, but the cost of any such extended warranties shall be borne solely out of the TI Fund. Landlord shall promptly undertake and complete, or cause to be completed, all punch list items.

(f) **Expansion Premises Commencement Date Delay**. Except as otherwise provided in the Lease, Delivery of the Expansion Premises shall occur when Landlord's Work has been Substantially

Completed, except to the extent that completion of Landlord's Work shall have been actually delayed by any one or more of the following causes ("**Tenant Delay**"):

(i) Tenant's Representative was not available within 3 business days to give or receive any Communication or to take any other action required to be taken by Tenant within the time period required hereunder;

(ii) Tenant's request for Change Requests (as defined in Section 4(a) below) whether or not any such Change Requests are actually performed;

(iii) Construction of any Change Requests;

(iv) Tenant's request for materials, finishes or installations requiring unusually long lead times;

(v) Tenant's delay in reviewing, revising or approving plans and specifications beyond the periods set forth herein;

(vi) Tenant's delay in providing information critical to the normal progression of Landlord's Work within the time period required hereunder (or, if no time period is provided for hereunder, 2 business days). Tenant shall provide such information as soon as reasonably possible, but in no event longer than one week after receipt of any request for such information from Landlord;

(vii) Tenant's delay in making payments to Landlord for Excess TI Costs (as defined in Section 5(e) below);

(viii) Labor disharmony as a result of non-union labor employed by any contractor or subcontractor engaged by Tenant or any Tenant Party; or

(ix) Any other act or omission by Tenant or any Tenant Party (as defined in the Lease), or persons employed by any of such persons that continues for more than 2 business days after Landlord's written notice thereof to Tenant.

If Delivery is delayed for any of the foregoing reasons, then Landlord shall cause the TI Architect to certify the date on which the Tenant Improvements would have been completed but for such Tenant Delay and such certified date shall be the date of Delivery.

4. **Changes**. Any changes requested by Tenant to the Tenant Improvements after the delivery and approval by Landlord of the TI Design Drawings shall be requested and instituted in accordance with the provisions of this Section 4 and shall be subject to the written approval of Landlord and the TI Architect, such approval not to be unreasonably withheld, conditioned or delayed.

(a) **Tenant's Request for Changes**. If Tenant shall request changes to the Tenant Improvements ("**Changes**"), Tenant shall request such Changes by notifying Landlord in writing in substantially the same form as the AIA standard change order form (a "**Change Request**"), which Change Request shall detail the nature and extent of any such Change. Such Change Request must be signed by Tenant's Representative. Landlord shall, before proceeding with any Change, use commercially reasonable efforts to respond to Tenant as soon as is reasonably possible with an estimate of: (i) the time it will take, and (ii) the architectural and engineering fees and costs that will be incurred, to analyze such Change Request (which costs shall be paid from the TI Fund to the extent actually incurred, whether or not

such change is implemented). Landlord shall thereafter submit to Tenant in writing, within 5 business days of receipt of the Change Request (or such longer period of time as is reasonably required depending on the extent of the Change Request), an analysis of the additional cost or savings involved, including, without limitation, architectural and engineering costs and the period of time, if any, that the Change will extend the date on which Landlord's Work will be Substantially Complete. Any such delay in the completion of Landlord's Work caused by a Change, including any suspension of Landlord's Work while any such Change is being evaluated and/or designed, shall be Tenant Delay.

(b) **Implementation of Changes**. If Tenant: (i) approves in writing the cost or savings and the estimated extension in the time for completion of Landlord's Work, if any, and (ii) deposits with Landlord any Excess TI Costs required in connection with such Change, Landlord shall cause the approved Change to be instituted. Notwithstanding any approval or disapproval by Tenant of any estimate of the delay caused by such proposed Change, the TI Architect's good faith determination of the amount of Tenant Delay in connection with such Change shall be final and binding on Landlord and Tenant.

5. **Costs**.

(a) **Budget For Tenant Improvements**. Before the commencement of construction of the Tenant Improvements, Landlord shall obtain a detailed breakdown by trade of the costs incurred or that will be incurred in connection with the design and construction of the Tenant Improvements (the "**Budget**"). The Budget shall be based upon the TI Construction Drawings approved by Tenant. If the Budget is greater than the TI Allowance, the TI Costs shall be funded on a *pari passu* basis as costs are incurred in accordance with Sections 5(e) and 5(f) below.

(b) **TI Allowance**. Landlord shall make available for the payment of the TI Costs a tenant improvement allowance Tenant a "**TI Allowance**" in the maximum amount of $[***] per rentable square foot of the Expansion Premises.

The TI Allowance shall be disbursed in accordance with this Expansion Premises Work Letter. Tenant shall have no right to the use or benefit (including any reduction to or payment of Base Rent) of any portion of the TI Allowance not required for the construction of (i) the Tenant Improvements described in the TI Construction Drawings approved pursuant to Section 2(d) or (ii) any Changes pursuant to Section 4.

(c) **Additional TI Allowance**. Landlord shall make available for the payment of Excess TI Costs an additional tenant improvement allowance (the "**Additional TI Allowance**") of $[***], which shall, to the extent used, result in TI Rent pursuant to Section 4(d) of the First Amendment. Within 5 business days of receipt of the Budget from Landlord, Tenant shall notify Landlord in writing how much of the Additional TI Allowance Tenant has elected to receive from Landlord (the "**Additional TI Allowance Election**"); provided, however that if Tenant does not elect the full amount of the Additional TI Allowance in the Additional TI Allowance Election, Tenant may elect to have additional funds, not to exceed any positive amount remaining after subtraction of the amount elected in the Additional TI Allowance Election from the Additional TI Allowance, to be made available to pay for Excess TI Costs (if any, the "**Subsequent Additional TI Allowance Election**"), upon 10 business days' prior written notice to Landlord, which prior written notice of any Subsequent Additional TI Allowance Election shall be given, if at all, within 45 days of the date of Tenant's initial Additional TI Allowance Election. The Subsequent Additional TI Allowance Election and Additional TI Allowance Election (or if no Subsequent Additional TI Allowance Election is made within the time period required, the Additional TI Allowance Election itself) shall be final and binding on Tenant, and may not thereafter be modified without Landlord's consent, which may be granted or withheld in Landlord's sole and absolute subjective discretion.

(d) **Costs Includable in TI Fund**. The TI Fund (as defined in Section 5(e) below) shall be used solely for the payment of design, permits and construction costs in connection with the construction

of the Tenant Improvements, including, without limitation, the cost of electrical power and other utilities used in connection with the construction of the Tenant Improvements, the cost of preparing the TI Design Drawings and the TI Construction Drawings, all costs set forth in the Budget, including Landlord's out-of-pocket expenses, costs resulting from Tenant Delays and the cost of Changes (collectively, "**TI Costs**"). Notwithstanding anything to the contrary contained herein, the TI Fund shall not be used to purchase any furniture, personal property or other non-building system materials or equipment, including, but not limited to, Tenant's voice or data cabling, non-ducted biological safety cabinets and other scientific equipment not incorporated into the Tenant Improvements.

(e) **Excess TI Costs**. Landlord shall have no obligation to bear any portion of the cost of any of the Tenant Improvements except to the extent of the TI Allowance and the Additional TI Allowance that Tenant has elected to receive. If at any time the remaining TI Costs under the then-current Budget exceed the remaining unexpended TI Allowance and Additional TI Allowance that Tenant has elected to receive (such excess sometimes referred to herein as "**Excess TI Costs**"), each party's obligations for payment shall be as set forth in this Section 5(e) and in Section 5(f). The TI Allowance, the Additional TI Allowance and Excess TI Costs are herein referred to as the "**TI Fund**." As used in this Work Letter, "**Landlord's Portion**" shall equal the TI Allowance and the Additional TI Allowance that Tenant has elected to receive. For purposes of this Work Letter, "**Landlord's Proportionate Share**" shall mean a fraction, the numerator of which shall be the Landlord's Portion and the denominator of which shall be the then-current Budget. If at any time TI Costs under the then-current Budget exceed the TI Allowance and the Additional TI Allowance that Tenant has elected to receive, the difference shall be referred to herein as "**Tenant's Portion**." For purposes of this Work Letter, "**Tenant's Proportionate Share**" shall mean a fraction, the numerator of which is Tenant's Portion and the denominator of which is the then-current Budget. Upon notice to Tenant, Landlord may equitably adjust Landlord's Proportionate Share and Tenant's Proportionate Share from time to time based on changes in the anticipated TI Costs. After the end of each calendar month, beginning with the month in which Landlord obtains the Budget: (i) Landlord shall determine the TI Costs incurred for the prior calendar month (and if applicable, for the period prior to Lease execution) (collectively, the "**Total Monthly Costs**"), (ii) Tenant shall reimburse Landlord within the time period set forth in Section 5(f) below for Tenant's Proportionate Share of Total Monthly Costs, and (iii) Landlord shall pay Landlord's Proportionate Share of Total Monthly Costs from the remaining amount of the TI Allowance and Additional TI Allowance that Tenant has elected to receive.

(f) **Funding Requisition; Reconciliation; Timely Payment**. Landlord shall submit to Tenant monthly during the performance of the Tenant Improvements a report (each, a "**Reimbursement Notice**") setting forth in reasonable detail: (i) a computation of the TI Costs incurred during the prior calendar month, including without limitation costs relating to all requested Changes; (ii) the then-current cumulative TI Costs; and (iii) Landlord's calculation of the parties' respective responsibilities for payment of such costs for such month (i.e., the estimated amounts of Tenant's Portion and/or Landlord's Portion due for such month). Each month, Landlord shall prepare a reconciliation of actual TI Costs with TI Costs in accordance with the Budget for which Tenant has advanced Tenant's Proportionate Share, and: (x) in the event of any overpayment by Tenant, then, solely to the extent of any Tenant's Proportionate Share that Tenant has actually deposited with Landlord, such overpayment shall be credited against the amounts next due hereunder unless construction of the Tenant Improvements is completed, in which case such overpayment shall be promptly refunded to Tenant; and (y) in the event of an underpayment by Tenant, Tenant shall, as a condition precedent to Landlord's obligation to complete the Tenant Improvements, reimburse Landlord therefor within thirty (30) days of receipt of a Reimbursement Notice. Notwithstanding anything to the contrary set forth in this Section, Tenant shall be fully and solely liable for TI Costs and the costs of Changes and Minor Variations in excess of the TI Allowance and Additional TI Allowance that Tenant has elected to receive. Reimbursement Notices may be sent during a calendar month for the prior calendar month and shall be submitted no later than the end of each calendar month for the prior calendar month. Upon final completion of the Tenant Improvements (including all Punch List Items), Landlord shall prepare a final reconciliation consisting of a reconciliation of the total costs of the Tenant Improvements. Tenant shall pay

to Landlord the amount of Tenant's Proportionate Share of Total Monthly Costs as set forth in each Reimbursement Notice within thirty (30) days of receipt of each Reimbursement Notice (or such lesser period as may be required to enable Landlord to comply with the Massachusetts "Prompt Pay" legislation). Such payment by Tenant shall be a condition precedent to Landlord's obligation to complete the Tenant Improvements. If Tenant fails to pay Tenant's Proportionate Share of Total Monthly Costs as set forth in any Reimbursement Notice within such period, Landlord shall have all of the rights and remedies set forth in the Lease for nonpayment of Rent (including, but not limited to, the right to interest at the Default Rate and the right to assess a late charge, each in accordance with the terms of the Lease). For purposes of any claims made or litigation instituted with regard to Tenant's Portion or Tenant's Proportionate Share of Total Monthly Costs, such amounts shall constitute Rent under the Lease.

6. **Tenant Access**.

(a) **Tenant's Access Rights**. Landlord hereby agrees to permit Tenant access, at Tenant's sole risk and expense, to the Expansion Premises (i) 60 days prior to the Expansion Premises Commencement Date to perform any work ("**Tenant's Work**") required by Tenant (including, without limitation, installing furniture, fixtures, equipment and cabling in the Premises) other than Landlord's Work, provided that such Tenant's Work is coordinated with the TI Architect and the General Contractor, and complies with the Lease and all other reasonable restrictions and conditions Landlord may impose, and (ii) prior to the completion of Landlord's Work, to inspect and observe work in process; all such access shall be during normal business hours or at such other times as are reasonably designated by Landlord. Any entry and access by Tenant shall comply with all established safety practices of the General Contractor and Landlord until completion of Landlord's Work and acceptance thereof by Tenant.

(b) **No Interference**. Neither Tenant nor any Tenant Party (as defined in the Lease) shall interfere with the performance of Landlord's Work, nor with any inspections or issuance of final approvals by applicable Governmental Authorities, and upon any such interference, Landlord shall have the right, in addition to other rights and remedies under the Expansion Premises Work Letter or the Lease, to exclude Tenant and/or any Tenant Party from the Expansion Premises until Substantial Completion of Landlord's Work.

(c) **Labor Harmony**. Tenant agrees that any work performed by or on behalf of Tenant or any Tenant Party shall be performed in such manner and by such persons as shall maintain harmonious labor relations at the Project. If labor disharmony arises as a result of non-union labor employed by a subcontractor or other contractor engaged by Tenant or any Tenant Party, and such labor disharmony causes a delay in the construction of the Non-TI Project Improvements or Landlord's Work, such delay shall be a Tenant Delay under this Work Letter. If labor disharmony arises as a result of a contractor or subcontractor engaged by Tenant or any Tenant Party, or if Landlord reasonably believes that a contractor or subcontractor employed by Tenant or any Tenant Party will cause labor disharmony in the Project, Landlord shall have the right, in addition to other rights and remedies under the Work Letter or Lease, to exclude from the Premises and Project such contractor or subcontractor employed by Tenant or any Tenant Party.

(d) **No Acceptance of Expansion Premises**. The fact that Tenant may, with Landlord's consent, enter into the Expansion Premises prior to the date Landlord's Work is Substantially Complete for the purpose of performing Tenant's Work shall not be deemed an acceptance by Tenant of possession of the Expansion Premises, but in such event Tenant shall defend with counsel reasonably acceptable by Landlord, indemnify and hold Landlord harmless from and against any loss of or damage to Tenant's property, completed work, fixtures, equipment, materials or merchandise, and from liability for death of, or injury to, any person, caused by the act or omission of Tenant or any Tenant Party.

7. **Miscellaneous**.

(a) **Consents**. Whenever consent or approval of either party is required under this Expansion Premises Work Letter, that party shall not unreasonably withhold, condition or delay such consent or approval, unless expressly set forth herein to the contrary.

(b) **Modification**. No modification, waiver or amendment of this Expansion Premises Work Letter or of any of its conditions or provisions shall be binding upon Landlord or Tenant unless in writing signed by Landlord and Tenant.

(c) **No Default Funding**. In no event shall Landlord have any obligation to fund any portion of the TI Allowance or to perform any Landlord's Work during any period that Tenant is in Default under the Lease.

Exhibit 10.12.1

*****Text Omitted and Filed Separately with the Securities and Exchange Commission. Confidential Treatment Requested Under 17 C.F.R. §200.80(b)(4)**

This SECOND AMENDMENT, effective as of July 25, 2018 (the "SECOND AMENDMENT EFFECTIVE DATE"), amends the Exclusive Patent License Agreement dated January 28, 2016, and First Amendment dated December 12, 2017 (the "LICENSE"), between the **Whitehead Institute for Biomedical Research** ("WHITEHEAD") and **Rubius Therapeutics, Inc.** ("COMPANY").

WHEREAS, WHITEHEAD and COMPANY wish to modify Appendix A of the LICENSE;

WHEREAS, WHITEHEAD is owner of certain SECOND AMENDMENT PATENT RIGHTS, as later defined herein, relating to [***], "[***]", by [***];

WHEREAS, WHITEHEAD desires to have the PATENT RIGHTS developed and commercialized to benefit the public, and WHITEHEAD is willing to grant a license thereunder;

WHEREAS, COMPANY desires to add such SECOND AMENDMENT PATENT RIGHTS to the LICENSE.

NOW, THEREFORE, WHITEHEAD and COMPANY hereby agree as follows:

Capitalized terms used herein and not defined herein shall have the respective meanings ascribed to such terms in the LICENSE.

1. The following (hereinafter the "SECOND AMENDMENT PATENT RIGHTS") is included under the definition of PATENT RIGHTS and is added to Appendix A of the LICENSE:

[***].

Appendix A of the LICENSE is deleted in its entirety and replaced with the Appendix A of this SECOND AMENDMENT, attached hereto.

2. For the avoidance of doubt, per Section 6.3 of the LICENSE, payment of all fees and costs, including attorneys' fees relating to the filing, prosecution, and maintenance of the SECOND AMENDMENT PATENT RIGHTS shall be the responsibility of COMPANY, whether such amounts were incurred before or after the SECOND AMENDMENT EFFECTIVE DATE. WHITEHEAD has incurred $[***] for such patent-related fees and costs as of [***].

3. The following is added to Section 10.1 of the LICENSE:

> 10.1 WHITEHEAD represents that as of the SECOND AMENDMENT EFFECTIVE DATE, it is the owner of all right, title, and interest in and to [***] of the PATENT RIGHTS, and it has the lawful right to grant the rights as set forth in this Agreement.

4. As consideration for this SECOND AMENDMENT, COMPANY shall pay WHITEHEAD a case addition fee of [***] Dollars ($[***]) within [***] of the SECOND AMENDMENT EFFECTIVE DATE. This payment is nonrefundable.

5. The LICENSE, as amended hereby, is hereby ratified and confirmed in all respects and shall continue in full force and effect. The LICENSE will, together with this SECOND AMENDMENT, be read and construed as a single instrument. All other terms and conditions of the LICENSE are confirmed and remain in full force and effect. This SECOND AMENDMENT shall be binding upon, and shall inure to the benefit of, the parties hereto and their respective successors and assigns.

Signatures follow on the next page.

IN WITNESS WHEREOF, the parties have caused this Agreement to be executed by their duly authorized representatives.

For WHITEHEAD		**For COMPANY:**	
By:	/s/ Carla DeMaria	By:	/s/ Torben Straight Nissen
Name:	Carla DeMaria	Name:	Torben Straight Nissen
Title:	Director of Intellectual Property & Sponsored Programs	Title:	President
Date:	July 31, 2018	Date:	July 25, 2018

APPENDIX A

List of Patent Applications and Patents

[***].

Exhibit 21.1

SUBSIDIARIES

Subsidiary	Jurisdiction of Incorporation
Rubius Therapeutics Securities Corporation	Massachusetts

Exhibit 23.1

CONSENT OF INDEPENDENT REGISTERED PUBLIC ACCOUNTING FIRM

We hereby consent to the incorporation by reference in the Registration Statement on Form S-8 (No. 333-226226) of Rubius Therapeutics, Inc. of our report dated March 28, 2019 relating to the financial statements, which appears in this Form 10-K.

/s/ PricewaterhouseCoopers LLP
Boston, Massachusetts
March 28, 2019

Exhibit 31.1

CERTIFICATION PURSUANT TO RULES 13a-14(a) AND 15d-14(a) UNDER THE SECURITIES EXCHANGE ACT OF 1934, AS ADOPTED PURSUANT TO SECTION 302 OF THE SARBANES-OXLEY ACT OF 2002

CERTIFICATIONS

I, Pablo J. Cagnoni, M.D., certify that:

1. I have reviewed this Annual Report on Form 10-K of Rubius Therapeutics, 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 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)):

(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) (Paragraph omitted pursuant to SEC Release Nos. 33-8238/34-47986 and 33-8392/34-49313);

(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 and I have disclosed, based on our most recent evaluation of internal control over financial reporting, to the registrant's auditors and the audit committee of the registrant's board of directors (or persons performing the equivalent functions):

(a) All significant deficiencies and material weaknesses in the design or operation of internal control over financial reporting which are reasonably likely to adversely affect the registrant's ability to record, process, summarize and report financial information; and

(b) Any fraud, whether or not material, that involves management or other employees who have a significant role in the registrant's internal control over financial reporting.

Date: March 28, 2019

By: /s/ Pablo J. Cagnoni
Pablo J. Cagnoni, M.D.
Chief Executive Officer
(Principal Executive Officer)

Exhibit 31.2

CERTIFICATION PURSUANT TO RULES 13a-14(a) AND 15d-14(a) UNDER THE SECURITIES EXCHANGE ACT OF 1934, AS ADOPTED PURSUANT TO SECTION 302 OF THE SARBANES-OXLEY ACT OF 2002

CERTIFICATIONS

I, Andrew M. Oh, certify that:

1. I have reviewed this Annual Report on Form 10-K of Rubius Therapeutics, 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 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)):

(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) (Paragraph omitted pursuant to SEC Release Nos. 33-8238/34-47986 and 33-8392/34-49313);

(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 and I have disclosed, based on our most recent evaluation of internal control over financial reporting, to the registrant's auditors and the audit committee of the registrant's board of directors (or persons performing the equivalent functions):

(a) All significant deficiencies and material weaknesses in the design or operation of internal control over financial reporting which are reasonably likely to adversely affect the registrant's ability to record, process, summarize and report financial information; and

(b) Any fraud, whether or not material, that involves management or other employees who have a significant role in the registrant's internal control over financial reporting.

Date: March 28, 2019

By: /s/ Andrew M. Oh
Andrew M. Oh
Chief Financial Officer
(Principal Financial Officer)

Exhibit 32.1

CERTIFICATION PURSUANT TO 18 U.S.C. SECTION 1350,

AS ADOPTED PURSUANT TO

SECTION 906 OF THE SARBANES-OXLEY ACT OF 2002

In connection with the Annual Report on Form 10-K of Rubius Therapeutics, 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, Pablo J. Cagnoni, M.D., Chief Executive Officer of the Company, hereby certifies, pursuant to 18 U.S.C. Section 1350, as adopted pursuant to Section 906 of the Sarbanes-Oxley Act of 2002, that to his knowledge:

(1) the Report fully complies with the requirements of Section 13(a) or 15(d) of the Securities Exchange Act of 1934; and

(2) the information contained in the Report fairly presents, in all material respects, the financial condition and results of operations of the Company.

Date: March 28, 2019

By: /s/ Pablo J. Cagnoni
Pablo J. Cagnoni, M.D.
Chief Executive Officer
(Principal Executive Officer)

Exhibit 32.2

CERTIFICATION PURSUANT TO 18 U.S.C. SECTION 1350,

AS ADOPTED PURSUANT TO

SECTION 906 OF THE SARBANES-OXLEY ACT OF 2002

In connection with the Annual Report on Form 10-K of Rubius Therapeutics, 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, Andrew M. Oh, Chief Financial Officer of the Company, hereby certifies, pursuant to 18 U.S.C. Section 1350, as adopted pursuant to Section 906 of the Sarbanes-Oxley Act of 2002, that to his knowledge:

(1) the Report fully complies with the requirements of Section 13(a) or 15(d) of the Securities Exchange Act of 1934; and

(2) the information contained in the Report fairly presents, in all material respects, the financial condition and results of operations of the Company.

Date: March 28, 2019

By: /s/ Andrew M. Oh
Andrew M. Oh
Chief Financial Officer
(Principal Financial Officer)