UNITED STATES
SECURITIES AND EXCHANGE COMMISSION
Washington, DC 20549

FORM 8-K/A

(Amendment No. 2)

CURRENT REPORT
Pursuant to Section 13 or 15(d)
of the Securities Exchange Act of 1934

Date of Report (Date of earliest event reported): June 29, 2023

Baudax Bio, Inc.

(Exact name of registrant as specified in its charter)

Pennsylvania	**001-39101**	**47-4639500**
(State or other jurisdiction of incorporation or organization)	**(Commission File Number)**	**(I.R.S. Employer Identification No.)**

490 Lapp Road, Malvern, Pennsylvania	**19355**
(Address of principal executive offices)	**(Zip Code)**

Registrant's telephone number, including area code: (484) 395-2470

Not Applicable
(Former name or former address, if changed since last report)

Check the appropriate box below if the Form 8-K filing is intended to simultaneously satisfy the filing obligation of the registrant under any of the following provisions (see General Instruction A.2. below):

☐ Written communications pursuant to Rule 425 under the Securities Act (17 CFR 230.425)

☒ Soliciting material pursuant to Rule 14a-12 under the Exchange Act (17 CFR 240.14a-12)

☐ Pre-commencement communications pursuant to Rule 14d-2(b) under the Exchange Act (17 CFR 240.14d-2(b))

☐ Pre-commencement communications pursuant to Rule 13e-4(c) under the Exchange Act (17 CFR 240.13e-4(c))

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

Title of Each Class	**Trading Symbol**	**Name of Exchange on Which Registered**
Common Stock, par value $0.01	BXRX	Nasdaq Capital Market

Indicate by check mark whether the registrant is an emerging growth company as defined in Rule 405 of the Securities Act of 1933 (§230.405 of this chapter) or Rule 12b-2 of the Securities Exchange Act of 1934 (§240.12b-2 of this chapter).

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. ☒

EXPLANATORY NOTE

On July 5, 2023, Baudax Bio, Inc., a Pennsylvania corporation (the "Company"), filed a Current Report on Form 8-K announcing that on June 29, 2023 (the "Effective Date"), the Company had acquired TeraImmune, Inc., a Delaware corporation ("TeraImmune") pursuant to that certain Agreement and Plan of Merger, dated as of the Effective Date (the "Merger Agreement") by and among the Company, Bounce Merger Sub I, Inc., a Delaware corporation and a wholly owned subsidiary of the Company ("First Merger Sub"), Bounce Merger Sub II, LLC, a Delaware limited liability company and wholly owned subsidiary of the Company ("Second Merger Sub"), and TeraImmune. This Current Report on Form 8-K/A amends and supplements the Current Report on Form 8-K filed on July 5, 2023 (the "July 2023 Form 8-K") to provide the Company's Business Section and Risk Factors Section.

The text of the July 2023 Form 8-K, as amended by Amendment No. 1 filed on July 31, 2023, is incorporated herein by reference. Capitalized terms not otherwise defined herein shall have the respective meanings ascribed to them in the July 2023 Form 8-K.

Item 8.01. Other Events.

The Company has updated the description of its Business and Risk Factors to provide updates relating to its merger with TeraImmune, each of which were included in the Company's preliminary proxy statement on Schedule 14A filed on July 31, 2023 and are filed herewith as Exhibits 99.1 and 99.2, respectively, and incorporated herein by reference.

Important Additional Information and Where to Find It

Baudax Bio, Inc., its directors and certain of its executive officers are deemed to be participants in the solicitation of proxies from Baudax Bio's shareholders in connection with the matters to be considered at Baudax Bio's 2023 Special Meeting of Shareholders. Information regarding the names of Baudax Bio's directors and executive officers and their respective interests in Baudax Bio by security holdings or otherwise can be found in Baudax Bio's proxy statement for its 2023 Annual Meeting of Shareholders, filed with the SEC on April 28, 2023. To the extent holdings of Baudax Bio's securities have changed since the amounts set forth in Baudax Bio's proxy statement for the 2023 Annual Meeting of Stockholders, such changes have been reflected on Initial Statements of Beneficial Ownership on Form 3 or Statements of Change in Ownership on Form 4 filed with the SEC. These documents are available free of charge at the SEC's website at www.sec.gov. Baudax Bio intends to file a proxy statement and accompanying proxy card with the SEC in connection with the solicitation of proxies from Baudax Bio shareholders in connection with the matters to be considered at Baudax Bio's 2023 Special Meeting of Shareholders. Additional information regarding the identity of participants, and their direct or indirect interests, by security holdings or otherwise, will be set forth in Baudax Bio's proxy statement for its 2023 Special Meeting of Shareholders, including the schedules and appendices thereto. **INVESTORS AND SHAREHOLDERS ARE STRONGLY ENCOURAGED TO READ ANY SUCH PROXY STATEMENT AND THE ACCOMPANYING PROXY CARD AND ANY AMENDMENTS AND SUPPLEMENTS THERETO AS WELL AS ANY OTHER DOCUMENTS FILED BY BAUDAX BIO WITH THE SEC CAREFULLY AND IN THEIR ENTIRETY WHEN THEY BECOME AVAILABLE AS THEY WILL CONTAIN IMPORTANT INFORMATION.** Shareholders will be able to obtain copies of the proxy statement, any amendments or supplements to the proxy statement, the accompanying proxy card, and other documents filed by Baudax Bio with the SEC for no charge at the SEC's website at www.sec.gov. Copies will also be available at no charge at the Investor Relations section of Baudax Bio's corporate website at https:// https://www.baudaxbio.com/news-and-investors.com or by contacting Baudax Bio's Investor Relations at Baudax Bio, Inc., 490 Lapp Road, Malvern, PA 19355 or by calling Baudax Bio's Investor Relations at (484) 395-2440.

Item 9.01. Financial Statements and Exhibits.

(d) Exhibits

EXHIBIT INDEX

Exhibit Number	Description
99.1	Business Section of Baudax Bio, Inc.
99.2	Risk Factors of Baudax Bio, Inc.
104	Cover Page Interactive Data File (embedded within the Inline XBRL document).

SIGNATURES

Pursuant to the requirements of the Securities Exchange Act of 1934, the registrant has duly caused this report to be signed on its behalf by the undersigned hereunto duly authorized.

Date: August 9, 2023

Baudax Bio, Inc.

By: /s/ Gerri A. Henwood
Name: *Gerri A. Henwood*
Title: *President and Chief Executive Officer*

Exhibit 99.1

DESCRIPTION OF BUSINESS OF BAUDAX BIO, INC.

Company Overview

Baudax Bio, Inc. is a biotechnology company focused on developing T cell receptor ("TCR") therapies utilizing human regulatory T cells ("Tregs"), as well as a portfolio of clinical stage Neuromuscular Blocking Agents ("NMBs") and an associated reversal agent. Our TCR Treg programs primarily focus on immune modulating therapies for orphan diseases or complications associated with such diseases, as well as the treatment of autoimmune disorders. We believe that our TCR Treg programs have the potential to provide valuable therapeutic options to patients suffering from diseases for which there are limited treatment options and significant unmet need, as well as to prescribers and payers in these markets.

On June 29, 2023, we acquired TeraImmune, Inc. ("TeraImmune"), a Delaware corporation. TeraImmune was a privately-held biotechnology company focused on discovery and development of novel Treg-based cell therapies for autoimmune diseases. TeraImmune's proprietary and patented technology platforms include a method for expansion of the Treg without losing its function and stability, as well as a method to target specific receptors including TCRs, Chimeric Antigen Receptors ("CARs") and B cell Antigen Receptors ("BARs"). TerraImmune has also in-licensed through an exclusive, sublicensable, royalty-bearing license, a patent family covering methods of producing T cell populations enriched for regulatory T cells and cell culture compositions from U.S. Department of Health and Human Services, as represented by National Institute of Allergy and Infectious Diseases of the National Institutes of Health. In addition, TeraImmune has developed Treg manufacturing procedures in accordance with regulatory guidance from the U.S. Food and Drug Administration ("FDA").

In June 2022, TeraImmune's Investigational New Drug ("IND") application to commence clinical trials of a Factor VIII ("FVIII") TCR-Treg treatment for Hemophilia A with inhibitors was cleared by the FDA.

Tregs are designed to recognize and target certain cells through the engagement of target-specific receptors by peptide antigens presented on the surface of the target cell by the major histocompatibility complex. Our proprietary and patented technology platform consists of two approaches: (1) TREGable™, which involves the isolation of natural Tregs, and (2) TREGing™, which involves engineering effector T ("Teff") cells into antigen-specific Tregs. Each approach is intended to recognize and attack pathogens while avoiding an attack on healthy cells and tissues. The lead product candidate we acquired in the acquisition with TeraImmune, TI-168, is being developed for the treatment of Hemophilia A with inhibitors, which received IND clearance in 2022. We have in-licensed two patent families relating to TI-168, nucleic acids constructs encoding T cell receptors, methods of producing TI-168, immunosuppressive induced regulatory T cells from the Henry M. Jackson Foundation for the Advancement of Military Medicine, Inc. ("HJF") under two worldwide, exclusive, sublicensable royalty-bearing licenses. We also exclusively license a family of pending U.S. and foreign patent applications directed to immunosuppressive induced regulatory T cells and methods of producing these cells, which if issued would expire in 2041 subject to any applicable disclaimer or extensions.

We also hold exclusive global rights to two new molecular entities, which are centrally acting NMBs, BX1000, an intermediate duration of action NMB that recently completed a successful Phase II clinical trial, and BX2000, an ultra-short acting NMB currently undergoing a Phase I clinical trial. A proprietary blockade reversal agent, BX3000, is currently being evaluated in preclinical studies intended to support an IND filing in 2023. BX3000 is an agent that is expected to rapidly reverse BX1000 and BX2000 blockade. All three agents are licensed from Cornell University. We believe these agents, when an NMB and BX3000 are administered in succession, allow for a rapid onset of centrally acting neuromuscular blockade, followed by a rapid reversal of the neuromuscular blockade with BX3000. These novel agents have the potential to meaningfully reduce time to onset and reversal of blockade and improve the reliability of onset and offset of neuromuscular blockade. This can potentially reduce time in operating rooms or post operative units, resulting in potential clinical and cost advantages, as well as valuable cost savings for hospitals and ambulatory surgical centers and has the potential for an improved clinical profile in terms of safety.

In mid-2020, we launched our first commercial product, ANJESO, in the United States. ANJESO was the first and only 24-hour, intravenous, analgesia agent. ANJESO is a cyclooxygenase-2 preferential, non-steroidal anti-inflammatory drug ("NSAID") for the management of moderate to severe pain, which could be administered alone or in combination with other non-NSAID analgesics. We discontinued commercial sales of ANJESO in December 2022 and further withdrew its New Drug Application ("NDA") related to ANJESO in late March 2023.

Our Strategy

We believe that we can bring valuable therapeutic options for patients suffering from certain orphan diseases and autoimmune disorders for which there are limited treatment options and significant unmet need, and prescribers and payers in these markets, as well as to the acute care and related markets. We believe we can create value for our shareholders through the development, and potential approval and commercialization of TI-168 for treatment of Hemophilia A with inhibitors, as well as our other pipeline product candidates we develop for the treatment of autoimmune disorders utilizing Treg-based therapies. In addition to our Treg pipeline, we continue to modestly progress the NMB and related assets, and will consider select acquisitions, especially those that could contribute revenue and cash flow.

Our near-term goals include:

- *Leveraging our development experience to progress TI-168, and the research experience of the TeraImmune team to progress additional Treg research product candidates.* We intend to leverage our drug development expertise to commence a Phase 1/2a clinical trial of TI-168 for treatment of the Hemophilia A with inhibitors, and continue development of TI-168 and other candidates for the treatment of other orphan or autoimmune disorders. We intend to approach the development of such programs in a cost-effective manner, including by potentially leveraging the data we generate from our TI-168 clinical trials for the further expansion of our Treg-based therapy platform, enabling us to expand our target indications and product candidates. Our overall goal is to utilize our drug development expertise to safely develop these Treg product candidates.

- *Continue development of our clinical stage NMB portfolio of product candidates.*Our legacy clinical stage product pipeline includes proprietary NMB blockade product candidates for use in anesthesia, BX1000 and BX2000, as well as an NMB reversal agent currently in preclinical studies, BX3000, which is currently being evaluated in preclinical studies intended to support an IND filing in the last quarter of 2023. We believe the concurrent development of a blocking agents and reversal agent used safely in the same patient, once certain stand alone and initial combination information is available, will allow our programs to provide clinical, financial, and temporal advantages to providers and patients.

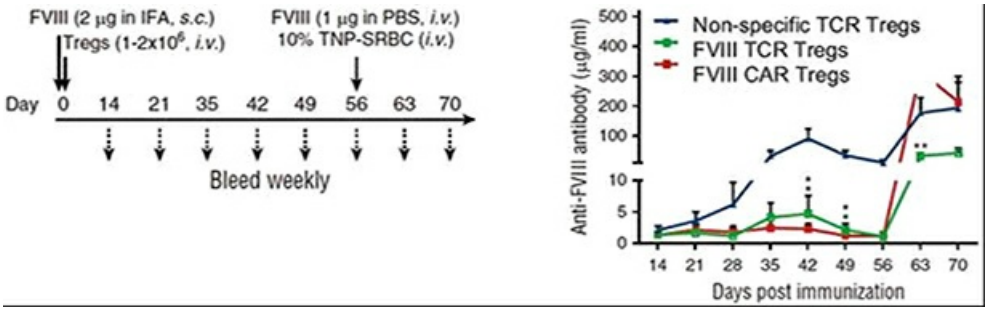
Products and Pipeline

Clinical Development

TI-168

Our lead Treg-based product candidate, TI-168, is being developed for the treatment of Hemophilia A with inhibitors. Hemophilia A is significant bleeding disorder characterized by impaired clotting as a result of deficiencies in the production or coagulation FVIII. Hemophilia A is an orphan disease that is lifelong and with limited treatment options. Approximately 30% of Hemophilia A patients develop inhibitors to FVIII, which can add complexity to its treatment regimen, and increase costs significantly. Inhibitors have historically been contraindicated with gene therapy, further limiting treatment options. The current standard of care for patients with FVIII inhibitors includes immune tolerance induction (“ITI”), along with the use of Emicizumab and bypass agents. We believe ITI therapy has important limitations, including that a significant portion of the patient population does not respond to ITI (up to 60%), recurrence can occur in a significant number of patients (up to 29%), the therapy can be expensive with respect to both time and resources, and may render a patient ineligible for gene therapy. We believe that TI-168, subject to FDA approval and commercialization, may provide Hemophilia A patients with the ability to avoid the potentially prohibitive cost, inconvenience, efficacy concerns and other limitations of ITI. Further, we believe that patients with FVIII tolerance that receive TI-168 will be potential candidates for gene therapy.

TI-168 is an autologous FVIII TCR-Treg cell therapy for the treatment of Hemophilia A patients with refractory inhibitors, which is designed to replace ITI treatments. Preclinical studies have shown that FVIII TCR-Tregs showed FVIII-specific immunosuppressive efficacy, with TCRs outperforming CAR Tregs. As illustrated in the images below, in a preclinical study, hemophilic mice were subcutaneously immunized for FVIII, and four hours thereafter, infused with either a TCR Treg, CAR Treg or nonspecific Treg. Over the course of the study, the nonspecific Treg could not effectively control the development of anti-FVIII antibodies, while the anti-FVIII antibody response was effectively suppressed by both the TCR and CAR Tregs over a period of approximately 8 weeks. Further, rechallenge with FVIII at day 56 resulted in a much higher loss of tolerance for the CAR Treg group, while the TCR Treg group's loss of tolerance remained significantly lower. We believe that FVIII TCR Tregs may provide a therapeutic option in controlling anti-FVIII antibody formation in refractory Hemophilia A patients, and have the potential to perform better than CAR Treg therapies.



We plan to initiate a Phase 1/2a clinical trial of TI-168 for the treatment of Hemophilia A with inhibitors, with proof of concept data expected on the first 3 patients within the next 12-15 months. We are actively engaging in the Institutional Review Board ("IRB") clinical trial site process. We intend to seek orphan drug designation in the United States for TI-168 for the treatment of Hemophilia A.

BX1000

We completed a Phase I study in 2021 for BX1000 which evaluated its safety profile when administered with Total Intravenous Anesthesia, as well as the dose response of neuromuscular blockade. We completed a dose-escalation study evaluating BX1000 in a total of 58 healthy volunteers who had already undergone endotracheal intubation while under general anesthesia. After intubation, subjects received a single IV bolus dose of BX1000 and were monitored for neuromuscular blockade and for any changes in vital signs or the presence of adverse events. BX1000 dose-escalations were continued until prespecified effects were observed. Doses of BX1000, up to 0.4 mg/kg, were well tolerated in this study of healthy volunteer subjects. Muscle paralysis was rapidly achieved along with complete spontaneous recovery. Neuromuscular blocking parameters were observed to increase in depth and duration of blockade while the time to onset of blockade was reduced with increasing doses of BX1000. Pharmacokinetic exposures increased with increasing study doses while elimination of the study compound remained rapid. Evaluation of electrocardiogram data using concentration-QTc modeling did not identify a risk of QTc prolongation within the studied dosing range. We engaged with the FDA regarding the design for the Phase II study in patients undergoing elective hernia and similar abdominal surgical procedures utilizing total intravenous anesthesia, in the fall of 2022, and initiated enrollment in the study in the fourth quarter of 2022. In January 2023, we announced the positive outcome of the interim analysis of the randomized, double blind, active controlled clinical Phase II trial, which compared three doses of BX1000 to a standard dose of rocuronium. The interim analysis was performed without breaking the study blind and was based on the first 20 of the 80 total patients being enrolled to the 4 study arms. The primary efficacy endpoint was the proportion of patients meeting criteria for Good or Excellent intubating conditions using a standardized scale. Additionally, the study is evaluating the safety and tolerability of BX1000 as compared to rocuronium in this patient population.

The top-line results for the Phase II clinical trial for BX1000 showed that BX1000 met the primary endpoint of readiness for intubation (evaluated as "Good" or "Excellent" - Viby-Mogensen 1996) at 60 seconds for all three dose levels of BX1000 compared to the active-control, rocuronium. Study treatments were generally well tolerated, with no occurrence of severe or serious adverse events. The frequency and severity of adverse events was similar across all four dose groups, and no notable events were aggregated in any one dose group.

BX2000

We filed an IND for BX2000 in 2020 in order to conduct a first-in-human clinical trial. We conducted an additional toxicology study requested by the FDA in 2021 and in March 2022, FDA notified us that we could proceed with initiation of a first in human, Phase I dose-escalation study in healthy volunteers.

In June of 2022, we announced the completion of dosing of the first cohort of the Phase I dose escalation study for BX2000, which we believe to be a rapid onset, ultra-short acting NMB agent, in healthy volunteers. The study is investigating single, ascending doses of BX2000 administered in a single, intravenous bolus injection compared to placebo. The study is comprised of up to 10 dosing cohorts and each cohort will enroll 8 patients. The study will evaluate the effect of BX2000 on safety, including heart rate, blood pressure, corrected QT interval, pharmacokinetics, and the time course of the neuromuscular blocking profile. Subjects will be monitored at an inpatient facility for 24 hours following administration of BX2000. There are also follow up visits on Day 8 and additional follow ups will take place approximately 2 and 4 weeks after dosing to evaluate the continued safety of study participants. Enrollment began in the second quarter of 2022 and cohort 2 completed, as planned, in the fourth quarter of 2022. Enrollment in cohort 3 was completed in 2023 and despite the challenges of enrollment to this type of protocol and operating on a limited budget, we remain optimistic that we will be close to reaching maximum dosage in 2024.

BX3000

BX3000 is a small molecule that was designed to induce chemical cleaving of BX1000 and BX2000, resulting in the rapid inactivation of those molecules and thus quickly reversing neuromuscular blockade. We are currently engaged with the pre-clinical toxicity studies needed to support an IND filing for BX3000 in the last quarter of 2023. We expect to begin the clinical program for BX3000 in 2023 within a limited budget.

Discovery platform

In addition to our named product candidates, we are actively engaged in a number of earlier stage discovery programs where we believe our Treg platform may provide therapeutic benefits. These discovery stage initiatives are focused on indications with pathological autoantibodies, including, among others, myasthenia gravis and multiple sclerosis. For these and other indications, we plan to use our Treg platform to develop therapeutics that could be used in the treatment of these, and other diseases involving pathological autoantibodies.

Licenses and Agreements

HA FVIII TCR Agreement

On August 5, 2019, TeraImmune entered into an exclusive worldwide license agreement (the "HA FVIII TCR Agreement") with HJF to utilize the licensed patent rights granted thereunder to research, design, develop, make, use, sell, distribute, exploit, improve and import the licensed products and processes covered thereby. The patent rights covered by the HA FVIII TCR Agreement include certain technologies relating to coagulation FVIII specific T cell receptors ("TCRs") or BAR expressing Tregs, methods of producing and stabilizing FVIII specific TCR or BAR expressing Tregs, and their use in humans. HJF retains the right to grant non-exclusive licenses to the patent rights covered under the HA FVIII TCR Agreement for non-commercial and research purposes. In addition, HJF retains the right to request that TeraImmune relinquish its exclusive rights under the HA FVIII TCR Agreement if it has not obtained FDA or other regulatory approval to a licensed product within ten years of the effective date of the HA FVIII TCR Agreement.

Pursuant to the HA FVIII TCR Agreement, TeraImmune has agreed to pay mid-single digit percent royalties on net sales (as defined therein) in jurisdictions where a valid claim with respect to the patent rights exist, and low-single digit percent royalties on net sales where no valid claim exists or where valid claims have expired. Additionally, TeraImmune agreed to pay a high-teens percentage of its non-royalty sublicense income received prior to regulatory approval of licensed product and a low-teens percentage of its non-royalty sublicense income received after regulatory approval of a licensed product, as well a minimal annual maintenance fee, which shall be credited against any royalty fees due and payable in for the calendar year relating to such maintenance fee. Further, TeraImmune is obligated to pay an aggregate of $1.3 million in milestone fees in the event such milestones are met. As of March 31, 2023, TeraImmune has paid a license royalty fee and annual royalties of $50,000 to HJF.

The HA FVIII TCR Agreement will remain in effect until the later of (a) the full end of the term or terms of certain patent rights as defined therein on a country-by-country basis or (b) 15 years from the first sale of the licensed product in a given country, whichever is longer, provided, however, that HJF may terminate the HA FVIII TCR Agreement in the event certain milestones are not met within the timeframe required by the HA FVIII TCR Agreement.

BML Agreement

On August 26, 2019, TeraImmune entered into the non-exclusive Biological Materials License Agreement (the "BMLA") with the National Cancer Institute ("NCI"), a part of the National Institutes of Health ("NIH"), which is part of the U.S. Government Department of Health and Human Services. Pursuant to the BMLA, TeraImmune was granted a world-wide, non-exclusive license to utilize the licensed patent rights granted thereunder to make, have made, use, sell and import autologous T cell therapy products for the treatment of Hemophilia A utilizing the pMSGV1 vector.

Pursuant to the BMLA, TeraImmune agreed to pay minimal non-refundable license, initial royalty, and annual royalty fees. Further, TeraImmune is required to pay a less than 1.0% royalty on net sales of any licensed products under the BMLA. As of March 31, 2023, TeraImmune has paid a license execution fee and annual royalties of $11,000 to NIH. The BMLA shall terminate in accordance with its terms ten years after the effective date thereof, unless extended by us and NCI.

HA ODN Agreement

On June 18, 2020, TeraImmune entered into an exclusive license agreement (the "HA ODN Agreement") with the National Institute of Allergy and Infectious Diseases ("NIAID"), a part of NIH. Pursuant to the HA ODN Agreement, TeraImmune was granted a non-exclusive license to utilize the licensed patent rights granted thereunder to make, have made, use, have used, sell and have sold, offer to sell and import certain autologous T cell therapy products for the treatment of Hemophilia A for patients who have inhibitory anti-FVIII auto-antibodies in the United States.

Pursuant to the HA ODN Agreement, TeraImmune agreed to pay mid-single digit percent royalties on net sales (as defined therein) of any licensed products covered by the HA ODN Agreement. TeraImmune also agreed to a minimal non-refundable license, initial royalty, and annual royalty fees. Additionally, TeraImmune agreed to reimburse NIAID for certain patent expenses on a payment schedule that may amount in total reimbursements of up to $45,000, including expenses incurred in maintaining the patent. As of March 31, 2023, TeraImmune has reimbursed an aggregate expense of $22,000 for patent prosecution fees and paid a license royalty fee and annual royalties of $33,000 to NIAID. The HA ODN Agreement also requires the payment of up to $1.1 million in milestone payments upon the achievement of certain regulatory and commercialization milestones. The HA ODN Agreement will remain in effect until the expiration of the last to expire of certain licensed patent rights or U.S. orphan drug exclusivity, each as defined therein, provided, however, that NIAID may terminate the HA ODN Agreement in the event that certain milestones are not met within the timeframe required by the HA ODN Agreement. *iTreg Agreement*

On November 11, 2020, TeraImmune entered into an exclusive worldwide license agreement (the "iTreg Agreement") with HJF to utilize the licensed patent rights granted thereunder to practice, research, design, develop, make, use, sell, distribute, exploit, improve and import the licensed products and processes covered thereby. The patents rights covered by the iTreg Agreement include technology related to inducable regulatory T ("iTreg") cells, methods for producing iTreg cells and their use in humans. TeraImmune agreed to take responsibility for the maintenance and prosecution of the Patent Rights in consultation with HJF on all strategic global filing and prosecution decisions. HJF retains the right to grant non-exclusive licenses to the patent rights covered by the iTreg Agreement for non-commercial and research purposes. In addition, HJF retains the right to request that TeraImmune relinquish its exclusive rights under the iTreg Agreement if it has not obtained FDA or other regulatory approval to a licensed product within six years of the effective date of the iTreg Agreement.

Pursuant to the iTreg Agreement, TeraImmune has agreed to pay low-single digit percent royalties to HJF on net sales (as defined therein) of any licensed product covered thereby and a low-teens percentage on its non-royalty sublicense income. TeraImmune paid a non-refundable license fee of $25,000 to HJF in December 2020. The iTreg Agreement will remain in effect until the full end of the term or terms of certain patent rights as defined therein on a country-by-country basis, provided, however, that HJF may terminate the iTreg Agreement in the event that certain milestones are not met within the timeframe required by the iTreg Agreement.

Intellectual Property

We license the patents and other intellectual property covering the NMBs and the related reversal agent and related methods of use under a worldwide, exclusive, sublicensable, royalty-bearing license from Cornell University. We exclusively license issued patents in the U.S. and other major foreign markets directed to BX1000 that expire in 2027, subject to any applicable disclaimer or extension, along with a pending PCT application directed to certain methods of using BX1000 that, if issued, would expire in 2041, subject to any applicable disclaimer or extension. We exclusively license issued patents in the U.S. and other major foreign markets directed to BX2000 that expire in 2033, subject to any applicable disclaimer or extension, along with a pending PCT application directed to certain methods of using BX-2000 that, if issued, would expire in 2041, subject to any applicable disclaimer or extension. Under the license agreement, we are obligated to pay Cornell University (i) an annual license maintenance fee payment which ranges from $15,000 to $125,000 until the first commercial sale of a licensed compound; (ii) milestone payments upon the achievement of certain milestones, up to a maximum, for each NMB, of $5 million for U.S. regulatory approval and commercialization milestones and $3 million for European regulatory approval and commercialization milestones; and (iii) royalties on net sales of the NMBs and the related reversal agent at rates ranging from low to mid-single digits, depending on the applicable licensed compound and whether there is a valid patent claim in the applicable country, subject to an annual minimum royalty amount of that increases after the fourth year of sales. In addition, we will reimburse Cornell University for past and ongoing patent costs related to prosecution and maintenance of the patents related to the licensed compounds. The license agreement is terminable by us at any time upon 90 days' written notice and by Cornell University upon our material breach, subject to a cure period, and upon our filing any claim asserting the invalidity of any of Cornell University's licensed patent rights. The royalty term for each licensed compound expires, on a country-by-country basis, on the later of (i) the expiration date of the longest-lived licensed patent, (ii) the expiration of any granted statutory period of marketing exclusivity, or (iii) the first commercial sale of a generic equivalent of the applicable licensed compound. On the last to expire royalty term the license agreement will automatically convert to a royalty-free nonexclusive license.

We have in-licensed a patent family covering methods of producing T cell populations enriched for regulatory T cells and cell culture compositions from U.S. Department of Health and Human Services, as represented by National Institute of Allergy and Infectious Diseases of the NIH under an exclusive, sublicensable royalty-bearing license. We exclusively license 2 issued U.S. patents covering methods of producing a population of cells having stable, regulatory T cells and cell culture compositions containing isolated human regulatory T cells, antibodies and an oligonucleotide that expire in 2033 subject to any applicable disclaimer or extensions. Under the license agreement with the NIH, we are obligated to pay the NIH (i) single-digit royalties on net sales subject a minimum annual royalty, which may be credited against royalties due for sales made in a particular year; and (ii) development milestone payments. Upon expiration of the licensed patent rights, a reduced royalty rate will be applied to net sales for the duration of the U.S. Orphan Drug Exclusivity period. The NIH license agreement is terminable by us at any time upon 60 days written notice and by the NIH if we fail in the performance of any material obligations under the license agreement subject to a cure period.

We have also in-licensed 2 patent families relating to TI-168, nucleic acids constructs encoding T cell receptors, methods of producing TI-168, immunosuppressive induced regulatory T cells and methods of producing these cells from HJF under two worldwide, exclusive, sublicensable royalty-bearing licenses. We exclusively license 2 issued patents in the U.S. and a pending European patent application relating to methods of producing and stabilizing T cell populations enriched for regulatory T cells and cell culture compositions that expire in 2034 subject to any applicable disclaimer or extension. We also exclusively license a family of pending U.S. and foreign patent applications directed to immunosuppressive induced regulatory T cells and methods of producing these cells which if issued would expire in 2041 subject to any applicable disclaimer or extensions. Under the license agreement with HJF, covering the 2 issued U.S. patents and pending European patent application, we are obligated to pay HJF (i) an annual license maintenance fee creditable against royalty payments due in the same year; (ii) single-digit royalties on net sales until expiration of the licensed patent rights, after which a reduced royalty rate will be applied to net sales for 15 years from the first sale of a licensed product; and (iii) development and funding milestone payments. Under the license agreement with HJF covering the pending U.S. and foreign patent applications directed to immunosuppressive induced regulatory T cells and methods of producing these cells, we are obligated to pay HJF single-digit royalties on net sales until expiration of the patent rights on a country-by-country basis. The HJF license agreements are terminable by us at any time upon 90 days written notice and by HJF if we fail in the performance of any obligations under the license agreement which in some instances are subject to a cure period.

We own patents and patent applications directed to the analgesia indication, formulations and intranasal methods of use of dexmedetomidine in the United States and certain major foreign markets. Several patents have issued outside the United States for transmucosal methods, and the resulting patent protection will last into 2030, subject to any disclaimers or extensions. In addition, patents related to intranasal methods has issued in the United States and certain major foreign markets, and the resulting patent protection will last into 2032, subject to any disclaimers or extensions.

We intend to rely on a combination of patents and trade secrets, as well as confidentiality agreements and license agreements, to protect our product candidates. Our patent strategy is designed to facilitate commercialization of our current product candidates and future product candidates, as well as create barriers to entry for third parties. One focus of our claim strategy is on formulation claims and other related claims.

We are seeking patent protection in the United States and internationally for our product candidates. Our policy is to pursue, maintain and defend patent rights and to protect the technology, inventions and improvements that are commercially important to the development of our business. 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 granted to us in the future will be commercially useful in protecting our technology. We also intend to rely on trade secrets to protect our product candidates. Our commercial success also depends in part on our non-infringement of the patents or proprietary rights of third parties.

Our success will depend significantly on our ability to:

- obtain and maintain patent and other proprietary protection for our product candidates, as well as obtaining and maintaining biologic product regulatory exclusivity for our products;
- defend our patents;
- develop trade secrets as needed and preserve the confidentiality of our trade secrets; and
- operate our business without infringing the patents and proprietary rights of third parties.

We have taken steps to build and will continue to build proprietary positions for our product candidates and related technology in the United States and abroad. We note that the patent laws of foreign countries differ from those in the United States, and the degree of protection afforded by foreign patents may be different from the protection offered by United States patents.

Government Regulation

Governmental authorities in the United States at the federal, state and local level, and the equivalent regulatory authorities in other countries, extensively regulate, among other things, the research, development, testing, manufacture, quality control, approval, labeling, packaging, storage, record-keeping, promotion, advertising, distribution, marketing, export and import of products such as those we are developing. Our product candidates must be approved by the FDA before they may legally be marketed in the United States. In addition, to the extent we choose to clinically evaluate or market any products in other countries or develop these products for future licensing to third parties, we are subject to a variety of regulatory requirements and to the authority of the competent regulatory authorities of those other countries.

U.S. Drug Development Process

In the United States, the FDA regulates drugs under the Federal Food, Drug, and Cosmetic Act ("FDCA") and implementing regulations. The process of obtaining regulatory approvals and ensuring compliance with appropriate federal, state, local and foreign statutes and regulations require 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 after approval, may subject an applicant to administrative enforcement or judicial sanctions. This enforcement could include, without limitation, the FDA's refusal to approve pending applications, withdrawal of an approval, a clinical hold, untitled or warning letters, corrective actions, product seizures, total or partial suspension of production or distribution, injunctions, fines, refusals of government contracts, restitution, disgorgement, or civil or criminal penalties.

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

- completion of preclinical laboratory tests, animal studies and formulation studies, some of which must be conducted according to good laboratory practices regulations;
- submission to the FDA of an IND, which must become effective before human clinical trials may begin;
- performance of adequate and well-controlled human clinical trials according to the FDA's good clinical practices ("GCPs") to establish the safety and efficacy of the proposed drug for its intended use;
- submission to the FDA of an NDA for a new drug or Biologics License Application ("BLA") for a new biologic product;
- satisfactory completion of an FDA pre-approval inspection of the manufacturing facility or facilities identified in the NDA or BLA;
- review and approval of proposed proprietary name; and
- FDA review and approval of the NDA or BLA.

The testing and approval process requires substantial time, effort and financial resources, and we cannot be certain that any approvals for our product candidates will be granted on a timely basis, if at all.

Once a pharmaceutical product candidate is identified for development, it enters the preclinical testing stage. Preclinical tests include laboratory evaluations of product chemistry, toxicity, formulation and stability, as well as animal studies. An IND sponsor must submit the results of the preclinical tests, together with manufacturing information, analytical data and any available clinical data or literature, to the FDA as part of the IND. The sponsor must also include a protocol detailing, among other things, the objectives of the initial clinical trial, the parameters to be used in monitoring safety, and the effectiveness criteria to be evaluated if the initial clinical trial lends itself to an efficacy evaluation. Some preclinical testing may continue even after the IND is submitted. The IND automatically becomes effective 30 days after receipt by the FDA, unless the FDA places the clinical trial on a clinical hold within that 30-day time period. In such a case, the IND sponsor and the FDA must resolve any outstanding concerns before the clinical trial can begin. Clinical holds also may be imposed by the FDA at any time before or during trials due to safety concerns regarding the product candidate or non-compliance with applicable requirements.

All clinical trials of a product candidate must be conducted under the supervision of one or more qualified investigators, in accordance with GCP regulations. These regulations include the requirement that all research subjects provide informed consent. Further, an IRB must review and approve the plan for any clinical trial before it commences at any institution. The IRB's role is to protect the rights and welfare of human subjects involved in clinical studies by evaluating, among other things, the potential risks and benefits to subjects, processes for obtaining informed consent, monitoring of data to ensure subject safety, and provisions to protect the subjects' privacy. The IRB approves the information regarding the clinical trial and the 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.

Once an IND is in effect, each new clinical protocol, and any amendments to the protocol, must be submitted to the IND for FDA review and to the IRBs for approval. Protocols detail, 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.

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

- Phase I. The product is initially introduced into healthy human subjects and tested for safety, dosage tolerance, absorption, metabolism, distribution and excretion. In the case of some products for severe or life-threatening diseases, especially when the product may be too inherently toxic to ethically administer to healthy volunteers, the initial human testing may be conducted in patients.

- Phase II. Phase II trials involve investigations in a limited patient population to identify possible adverse effects and safety risks, to preliminarily evaluate the efficacy of the product for specific targeted indications and to determine dosage tolerance and optimal dosage and schedule.

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

Progress reports detailing the results of the clinical trials must be submitted at least annually to the FDA, and safety reports must be submitted to the FDA and the investigators for serious and unexpected side effects. Phase I, Phase II and Phase III testing may not be completed successfully within any specified period, if at all. Results from earlier trials are not necessarily predictive of results from later trials. 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 has been associated with unexpected serious harm to patients.

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

U.S. Review and Approval Processes

The results of product development, preclinical studies and clinical trials, along with descriptions of the manufacturing process, analytical tests conducted on the drug, proposed labeling and other relevant information, are submitted to the FDA as part of an NDA for a new drug or BLA for a new biologic agent, requesting approval to market the product.

The submission of an NDA generally is subject to the payment of a substantial user fee for a human drug application. In addition, under the Pediatric Research Equity Act of 2003, an NDA or supplement to an NDA for a new indication, dosage form, dosing regimen, route of administration, or active ingredient, must contain data to assess the safety and effectiveness of the drug for the claimed indications in all relevant pediatric subpopulations and to support dosing and administration for each pediatric subpopulation for which the product is safe and effective. The FDA may waive or defer pediatric studies under certain circumstances.

Section 505(b)(2) New Drug Applications. As an alternate path to FDA approval, particularly for modifications to drug products previously approved by the FDA, an applicant may submit an NDA under Section 505(b)(2) of the FDCA ("Section 505(b)(2) NDA"). Section 505(b)(2) was enacted as part of the Drug Price Competition and Patent Term Restoration Act of 1984, commonly referred to as the Hatch-Waxman Amendments, and it permits approval of applications other than those for duplicate products and permits reliance for such approvals on literature or on the FDA's findings of safety and effectiveness of an approved drug product. A Section 505(b)(2) NDA is an application where at least some of the information required for approval comes from clinical trials not conducted by or for the applicant and for which the applicant has not obtained a right of reference. The FDA requires submission of information needed to support any changes relative to a previously approved drug, known as the reference product, such as published data or new studies conducted by the applicant, including bioavailability or bioequivalence studies, or clinical trials demonstrating safety and effectiveness. The FDA may then approve the Section 505(b)(2) NDA for all or some of the labeled indications for which the reference product has been approved, as well as for any new indication sought by the applicant, unless such indications or uses are protected by patent or exclusivity provisions covering the reference product. To the extent that a Section 505(b)(2) NDA relies on clinical trials conducted for a previously approved drug product or the FDA's prior findings of safety and effectiveness for a previously approved drug product, the Section 505(b)(2) applicant must submit patent certifications in its application with respect to any patents for the reference product that are listed in the FDA's publication, Approved Drug Products with Therapeutic Equivalence Evaluations, commonly referred to as the Orange Book. Specifically, the applicant must certify for each listed patent that, in relevant part, (1) the required patent information has not been filed; (2) the listed patent has expired; (3) the listed patent has not expired but will expire on a particular date and approval is not sought until after patent expiration; or (4) the listed patent is invalid, unenforceable or will not be infringed by the proposed new product. A certification that the new product will not infringe the previously approved product's listed patent or that such patent is invalid or unenforceable is known as a Paragraph IV certification. If the applicant does not challenge one or more listed patents through a Paragraph IV certification, the FDA will not approve the Section 505(b)(2) NDA until all the listed patents claiming the referenced product have expired.

Further, the FDA will also not approve a Section 505(b)(2) NDA until any non-patent exclusivity, such as, for example, five-year exclusivity for obtaining approval of a new chemical entity, three-year exclusivity for an approval based on new clinical trials, or pediatric exclusivity, listed in the Orange Book for the reference product, has expired.

If the Section 505(b)(2) NDA applicant has provided a Paragraph IV certification to the FDA, the applicant must also send notice of the Paragraph IV certification to the owner of the reference product and relevant patent holders within 20 days after the Section 505(b)(2) NDA has been accepted for filing by the FDA. The NDA and patent holders may then initiate a patent infringement suit against the Section 505(b)(2) applicant. Under the FDCA, the filing of a patent infringement lawsuit within 45 days of receipt of the notification regarding a Paragraph IV certification automatically prevents the FDA from approving the Section 505(b)(2) NDA for 30 months, beginning on the date the patent holder receives notice, or until the patent expires or a court deems the patent unenforceable, invalid or not infringed, whichever is earlier. Even if a patent infringement claim is not brought within the 45-day period, a patent infringement claim may be brought under traditional patent law, but it does not invoke the 30-month stay. Moreover, in cases where a Section 505(b)(2) application containing a Paragraph IV certification is submitted after the fourth year of a previously approved drug's five-year exclusivity period, and the patent holder brings suit within 45 days of notice of certification, the 30-month period is automatically extended to prevent approval of the Section 505(b)(2) application until the date that is seven and one-half years after approval of the previously approved reference product. The court also has the ability to shorten or lengthen either the 30-month or the seven and one-half year period if either party is found not to be reasonably cooperating in expediting the litigation. Thus, the Section 505(b)(2) applicant may invest a significant amount of time and expense in the development of its product only to be subject to significant delay and patent litigation before its product may be commercialized. Alternatively, if the NDA applicant or relevant patent holder does not file a patent infringement lawsuit within the specified 45-day period, the FDA may approve the Section 505(b)(2) application at any time, assuming the application is otherwise approvable.

Notwithstanding the approval of many products by the FDA pursuant to Section 505(b)(2), over the last few years, some pharmaceutical companies and other stakeholders have objected to the FDA's interpretation of Section 505(b)(2). If the FDA changes its interpretation of Section 505(b)(2), or if the FDA's interpretation is successfully challenged in court, this could delay or even prevent the FDA from approving any Section 505(b)(2) NDA that we submit.

FDA Review of New Drug Applications. The FDA reviews all NDAs submitted to ensure that they are sufficiently complete for substantive review before it accepts them for filing. If the FDA does not find an NDA to be sufficiently complete for filing, it may request additional information rather than accepting the NDA for filing. In this event, the sponsor must resubmit the NDA with the additional information. The re-submitted application also is subject to review before the FDA accepts it for filing. Once the submission is accepted for filing, the FDA begins an in-depth substantive review. The FDA reviews an NDA to determine, among other things, whether clinical data demonstrates that a product is safe and effective for its intended use and whether its manufacturing process can assure the product's identity, strength, quality and purity. Before approving an NDA, the FDA will inspect the facility or facilities where the product is manufactured. The FDA will not approve an application unless it determines that the manufacturing processes and facilities are in compliance with cGMP requirements and adequate to assure consistent production of the product within required specifications. The FDA may refer the NDA to an advisory committee for review, evaluation and recommendation as to whether the application should be approved and under what conditions. An advisory committee is a panel of independent experts who provide advice and recommendations when requested by the FDA. The FDA is not bound by the recommendation of an advisory committee.

The approval process is lengthy and difficult, and the FDA may refuse to approve an NDA if the applicable regulatory criteria are not satisfied or may require additional clinical data or other data and information. Even if such data and information are submitted, the FDA may ultimately decide that the NDA 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. The FDA will issue a complete response letter ("CRL") if the agency decides not to approve the NDA in its present form. The CRL usually describes all the specific deficiencies that the FDA identified in the NDA. The deficiencies identified may be minor, for example, requiring labeling changes, or major, for example, requiring additional clinical trials. Additionally, the CRL may include recommended actions that the applicant might take to place the application in a condition for approval. If a CRL is issued, the applicant may either resubmit the NDA, addressing all the deficiencies identified in the letter, withdraw the application or request an opportunity for a hearing.

If a product receives regulatory approval, the approval may be significantly limited to specific diseases and dosages, or the indications for use may otherwise be limited, which could restrict the commercial value of the product. Further, the FDA may require that certain contraindications, warnings or precautions be included in the product labeling, and the agency also may require a risk evaluation and mitigation strategy ("REMS") if it determines that a REMS is necessary to assure that the benefits of a drug outweigh its risks. In addition, the FDA may require Phase IV testing, which involves clinical trials designed to further assess a drug's safety and effectiveness after NDA approval, and may require testing and surveillance programs to monitor the safety of approved products that have been commercialized.

U.S. Biologic nonclinical and clinical development

Prior to beginning the first clinical trial with a biologic product candidate in the U.S., we must submit an IND to the FDA. An IND is a request for authorization from the FDA to administer an investigational new drug product to humans. The IND includes the clinical protocols and general development plan, as well as results of animal and in vitro studies assessing the toxicology, pharmacokinetic ("PK"), pharmacology and PD characteristics of the product candidate; chemistry, manufacturing, and controls information; and any available human data or literature to support the use of the investigational product. An IND must become effective before human clinical trials may begin. The IND automatically becomes effective 30 days after receipt by the FDA, unless the FDA, within the 30-day time period, raises concerns or questions. In such a case, the IND may be placed on clinical hold until the IND sponsor and the FDA resolve the outstanding concerns or questions. The FDA also may impose clinical holds at any time before or during clinical studies due to safety concerns or non-compliance. If the FDA imposes a clinical hold, studies may not recommence without FDA authorization and then only under terms authorized by the FDA. Submission of an IND therefore does not guarantee that FDA authorization to begin a clinical trial will be granted or that, once begun, issues will not arise that adversely impact, suspend or terminate such studies.

Clinical trials involve the administration of the investigational product to human subjects under the supervision of qualified investigators in accordance with GCPs, which include the requirement that all research subjects provide their informed consent for their participation in any clinical study. Clinical trials are conducted under protocols detailing, among other things, the objectives of the study, the parameters to be used in monitoring safety and the effectiveness criteria to be evaluated. A separate submission to the existing IND must be made for each successive clinical trial conducted during product development and for any subsequent protocol amendments and additional information such as toxicology or Chemistry, Manufacturing and Controls data in support of the investigational product(s). For new indications, a separate new IND is usually required. Outside of the U.S., clinical trial applications are generally required to conduct clinical studies in each country. Furthermore, an independent IRB for each site proposing to conduct the clinical trial must review and approve the plan for any clinical trial and its informed consent form before the clinical trial begins at that site, and must monitor the study until completed to ensure that the risks to individuals participating in the clinical trials are minimized and are reasonable in relation to anticipated benefits.

Regulatory authorities, the IRB or the sponsor may suspend a clinical trial at any time on various grounds, including a finding that the subjects are being exposed to an unacceptable health risk or that the trial is unlikely to meet its stated objectives. Some studies also include oversight by an independent group of qualified experts organized by the clinical study sponsor, known as a data safety monitoring board or independent data monitoring committee, which provides direction for whether or not a study may move forward at designated check points based on access to certain data from the study and may halt the clinical trial if it determines that there is an unacceptable safety risk for subjects or other grounds, such as no demonstration of efficacy. There are also requirements governing the reporting of ongoing clinical studies and clinical study results to public registries.

Information about most clinical trials must be submitted within specific timeframes for publication on thewww.clinicaltrials.gov website. For purposes of BLA/market authorization application approval, human clinical trials are typically conducted in three sequential phases that may overlap or be combined.

- Phase 1 — The investigational product is initially introduced into healthy human subjects or patients with the target disease or condition. These studies are designed to test the safety, tolerability, absorption, metabolism, distribution and elimination of the investigational product in humans, the side effects associated with increasing doses, and, if possible, to gain early evidence on pharmacodynamics and effectiveness.

- Phase 2 — The investigational product is administered to a limited patient population with a specified disease or condition to evaluate the preliminary efficacy, optimal dosages and dosing schedule and to identify possible adverse side effects and safety risks. Multiple Phase 2 clinical trials may be conducted to obtain information prior to beginning larger and more expensive Phase 3 clinical trials.

- Phase 3 — The investigational product is administered to an expanded patient population to further evaluate dosage, to provide statistically significant evidence of clinical efficacy and to further test for safety, generally at multiple global clinical trial sites. These clinical trials are intended to establish the overall risk/benefit ratio of the investigational product and to provide an adequate basis for product approval. These trials may include comparisons with placebo and/or other comparator treatments. The duration of treatment is often extended to support chronic use of a product during marketing.

In some cases, the FDA may require, or companies may voluntarily pursue, additional clinical trials after a product is approved to gain more information about the product. These so-called Phase 4 studies may be made a condition to approval of the BLA or, in certain circumstances, mandated after approval. These trials are used to gain additional experience from the treatment of patients in the intended therapeutic indication and are commonly intended to generate additional safety data regarding use of the product in a clinical setting or in some cases to support full approval for products that are approved via an accelerated pathway as described below. During all phases of clinical development, regulatory agencies require extensive monitoring and auditing of all clinical activities, clinical data, and clinical study investigators. Annual progress reports detailing the results of the clinical studies must be submitted to the FDA, and IND safety reports must be submitted to the FDA, other regulators, and investigators within a regulated timeframe for serious and unexpected adverse events, any findings from other studies, tests in laboratory animals or in vitro testing that suggest a significant risk for human subjects, or any clinically important increase in the rate of a serious suspected adverse reaction over that listed in the protocol or investigator brochure or adverse events reported by anti-FcRn product candidates developed by others.

Concurrent with clinical trials, companies may complete additional animal studies and develop additional information about the biological characteristics of the product candidate and must finalize a process for manufacturing the product in commercial quantities in accordance with cGMP requirements. The manufacturing process must be capable of consistently producing quality batches of the product candidate and, among other things, must develop methods for testing the identity, strength, quality and purity of the final product, or for biologics, the safety, purity and potency. The FDA may require such testing to occur on a lot-by-lot basis in order to release product for clinical use. Additionally, appropriate packaging must be selected and tested, and stability studies must be conducted to demonstrate that the product candidate does not undergo unacceptable deterioration over its shelf life.

BLA Submission, Review and Approval

Assuming successful completion of all required testing in accordance with all applicable regulatory requirements, the results of product development, nonclinical studies and clinical trials are submitted to the FDA as part of a BLA requesting approval to market the product for one or more indications. The BLA must include all relevant data available from pertinent preclinical and clinical studies, including negative or ambiguous results as well as positive findings, together with detailed information relating to the product's chemistry, manufacturing, controls, and proposed labeling, among other information. Data obtained from clinical trials are not always conclusive and the FDA may interpret data differently than we interpret the same data. The submission of a BLA requires payment of a substantial application user fee to FDA, unless a waiver or exemption applies. There can be no assurance that the FDA will accept the BLA for filing and, even if filed, that any approval will be granted on a timely basis, if at all.

Once a BLA has been submitted, the FDA reviews the BLA within 60 days to determine if it is substantially complete before the agency accepts it for filing. The FDA may refuse to file any BLA that it deems incomplete or not properly reviewable at the time of submission and may request additional information. In this event, the BLA must be resubmitted with the additional information. The resubmitted application also is subject to review before the FDA accepts it for filing. Under the goals and policies agreed to by the FDA under the Prescription Drug User Fee Act ("PDUFA"), the FDA's goal is to review standard applications within ten months after it accepts the application for filing, or, if the application qualifies for priority review, six months after the FDA accepts the application for filing. In both standard and priority reviews, the FDA does not always meet PDUFA goal dates, and the review process can be significantly extended by FDA requests for additional information or clarification or company submissions of substantial data during the review. The FDA reviews a BLA to determine, among other things, whether a product is safe, pure and potent and the facility in which it is manufactured, processed, packed, or held meets standards designed to assure the product's continued safety, purity and potency. The FDA may convene an advisory committee to provide clinical insight on application review questions with emphasis on risk and benefit of the molecule and proposed indications, and provide a recommendation as to whether the application should be approved and under what conditions. The FDA is not bound by the recommendations of an advisory committee, but it considers such recommendations carefully when making decisions. Before approving a BLA, the FDA will typically inspect the facility or facilities where the product is manufactured. The FDA will not approve an application unless it determines that the manufacturing processes and facilities are in compliance with cGMP requirements and adequate to assure consistent production of the product within required specifications. Additionally, before approving a BLA, the FDA will typically inspect one or more clinical sites, preclinical studies, and/or the sponsor to assure compliance with GCP. If the FDA determines that the application, manufacturing process or manufacturing facilities are not acceptable, it will outline the deficiencies in the submission and often will request additional testing or information. Notwithstanding the submission of any requested additional information, the FDA ultimately may decide that the application does not satisfy the regulatory criteria for approval.

After the FDA evaluates a BLA and conducts inspections of manufacturing facilities where the investigational product and/or its drug substance will be produced, the FDA may issue an approval letter or a Complete Response letter. An approval letter authorizes commercial marketing of the product with specific prescribing information for specific indications. A Complete Response letter will describe all of the deficiencies that the FDA has identified in the BLA, and where the FDA determines that the data supporting the application are inadequate to support approval, the FDA may issue the Complete Response letter prior to inspections, testing submitted product lots, and/or reviewing proposed labeling. In issuing the Complete Response letter, the FDA may recommend actions that the applicant might take to place the BLA in condition for approval, including requests for additional information or clarification, completion of other significant and time-consuming requirements related to clinical trials, and/or conduct of additional preclinical studies or manufacturing activities. Even if such data and information are submitted, the FDA may determine that the BLA does not satisfy the criteria for approval. FDA approval of a BLA must be obtained before a biologic may be marketed in the U.S. The FDA may delay or refuse approval of a BLA if applicable regulatory criteria are not satisfied and may require additional clinical testing or safety information.

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, which could limit the commercial value of the product. For example, the FDA may approve the BLA with a 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 product, and could include medication guides, healthcare professional and/or patient communication plans, or elements to assure safe use, such as restricted distribution methods, patient registries and other risk minimization tools. The FDA will evaluate if any labeling or risk management plans are necessary to ensure safe use of the product in the targeted patient population and indication. Once approved, the FDA has the authority to 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 impose post-marketing requirements and commitments such as additional manufacturing data or testing; additional preclinical data or evaluation; additional clinical data from Phase 3 studies (e.g. long-term extension data); and may require one or more Phase 4 post-market studies and 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.

Expedited Development and Review Programs and other Marketing Authorization Procedures

Any marketing application for a biologic submitted to the FDA for approval may be eligible for FDA programs intended to expedite the FDA review and approval process, such as priority review, fast track designation, breakthrough therapy and accelerated approval.

A product is eligible for priority review if it is intended to treat a serious condition and, if approved, would provide a significant improvement in safety or effectiveness. Priority review designation means the FDA's goal under PDUFA is to take action on the marketing application within six months of the 60-day filing date (compared with ten months under standard review). To be eligible for a fast track designation, the FDA must determine, based on the request of a sponsor, that a product is intended to treat a serious or life threatening disease or condition and demonstrates the potential to address an unmet medical need by providing a therapy where none exists or a therapy that may be potentially superior to existing therapy based on efficacy or safety factors. Fast track designation is intended to facilitate development and expedite review of a product, and also provides opportunities for frequent interactions with the FDA review team. The FDA may also review complete sections of the BLA for a fast track product on a rolling basis before the entire application is submitted, if the sponsor and FDA agree on a schedule for the submission of the application sections, and the sponsor pays any required user fees upon submission of the first section of the BLA. The review clock generally does not begin until the final section of the BLA is submitted.

In addition, a sponsor can request designation of a product candidate as a "breakthrough therapy." A breakthrough therapy is defined as a drug or biologic that is intended, alone or in combination with one or more other drugs or biologics, to treat a serious or life-threatening disease or condition, and preliminary clinical evidence indicates that the drug or biologic may demonstrate substantial improvement over existing therapies on one or more clinically significant endpoints, such as substantial treatment effects observed early in clinical development. The FDA will 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.

Additionally, products studied for their safety and effectiveness in treating serious or life-threatening diseases or conditions and that provide meaningful therapeutic benefit over existing treatments may receive accelerated approval, which means that they may be approved on the basis of adequate and well-controlled clinical studies establishing that the product has an effect on a validated surrogate endpoint that is reasonably likely to predict a clinical benefit, or on the basis of an effect on a clinical endpoint that can be measured earlier than survival or irreversible morbidity and is reasonably likely to predict an effect on survival, irreversible morbidity or another clinical benefit. As a condition of accelerated approval, the FDA requires the sponsor to perform adequate and well-controlled post-marketing confirmatory clinical studies to verify and describe the anticipated effect on irreversible morbidity or mortality or other clinical benefit. Approval may be withdrawn if the confirmatory study does not verify the anticipated clinical benefit. In addition, the FDA currently requires as a condition for accelerated approval pre-approval of promotional materials, which the sponsor must plan to provide all commercial materials and seek approval prior to the launch of the product.

Even if a product qualifies for one or more of these programs, the FDA may later decide that the product no longer meets the conditions for qualification or decide that the time period for FDA review and approval will not be shortened. Furthermore, priority review, fast track designation, breakthrough therapy designation, and accelerated approval do not change the standards for approval and may not ultimately expedite the development or approval process.

Orphan Drug Designation

Under the Orphan Drug Act, the FDA may grant orphan designation to a drug or biologic intended to treat a rare disease or condition, which is a disease or condition that affects fewer than 200,000 individuals in the U.S., or more than 200,000 individuals in the U.S. for which there is no reasonable expectation that the cost of developing and making available in the U.S. a drug or biologic for this type of disease or condition will be recovered from sales in the U.S. for that drug or biologic. Orphan designation must be requested before submitting a BLA. After the FDA grants orphan designation, the generic identity of the therapeutic agent and its potential orphan use are disclosed publicly by the FDA. The orphan drug designation does not convey any advantage in, or automatically shorten the duration of, the regulatory review or approval process. If a product that has orphan designation subsequently receives the first FDA approval for the disease for which it has such designation, the product is entitled to orphan exclusivity, which means that the FDA may not approve any other applications, including a full BLA, to market the same product 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 by means of greater effectiveness, greater safety or providing a major contribution to patient care or in instances of drug supply issues. Orphan exclusivity does not prevent FDA from approving a different drug or biologic for the same disease or condition, or the same drug or biologic for a different disease or condition. Among the other benefits of orphan drug designation are tax credits for certain research and a waiver of the BLA application fee. A designated orphan product may not receive orphan exclusivity if it is approved for a use that is broader than the indication for which it received orphan designation. In addition, exclusive marketing rights in the U.S. may be lost if the FDA later determines that the request for designation was materially defective or if the manufacturer is unable to assure sufficient quantities of the product to meet the needs of patients with the rare disease or condition.

Biosimilars and Reference Product Exclusivity

The Patient Protection and Affordable Care Act (“Affordable Care Act”) signed into law in 2010 includes a subtitle called the Biologics Price Competition and Innovation Act of 2009 (“BPCIA”), which created an abbreviated approval pathway for biological products that are biosimilar to or interchangeable with an FDA-approved reference biological product. To date, a number of biosimilars have been licensed under the BPCIA, but no interchangeable biologic has been approved in the U.S. The FDA has issued several guidance documents outlining its approach to the review and approval of biosimilars. Biosimilarity, 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 biological product and the reference product in terms of safety, purity, and potency, can be shown through analytical studies, animal studies, and a clinical study or studies. Interchangeability requires that a product is biosimilar to the reference product and the product must demonstrate that it can be expected to produce the same clinical results as the reference product in any given patient and, for products that are administered multiple times to an individual, the biologic and the reference biologic 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 biologic. Under the BPCIA, an application for a biosimilar product may not be submitted to the FDA until four years following the date that the reference product was first licensed by the FDA. In addition, the approval of a biosimilar product may not be made effective by the FDA until 12 years from the date on which the reference product was first licensed. During this 12-year period of exclusivity, another company may still market a competing version of the reference product if the FDA approves a full BLA for the competing product containing that applicant’s own preclinical data and data from adequate and well-controlled clinical trials to demonstrate the safety, purity and potency of its product. The BPCIA also created certain exclusivity periods for biosimilars approved as interchangeable products.

Patent Term Restoration and Marketing Exclusivity

Depending upon the timing, duration and specific circumstances of FDA marketing approval of our product candidates, some of our U.S. patents may be eligible for limited patent term extension under the Hatch-Waxman Amendments. The Hatch-Waxman Amendments permit a patent restoration term of up to five years for patent term lost during product development and the FDA regulatory review process. However, patent term restoration cannot extend the remaining term of a patent beyond a total of 14 years from the product's approval date. Subject to certain limitations, the patent term restoration period is generally equal to one-half of the time between the effective date of an IND and the submission date of an NDA, plus the time between the submission date of an NDA and the approval of that application. However, each phase of the regulatory review period may be reduced by any time that the FDA finds the applicant did act not act with due diligence. Only one patent applicable to an approved drug is eligible for the extension, it must be the first approval of the active ingredient of the product, and the application for the extension must be submitted prior to the expiration of the patent and within sixty days of approval of the drug. The U.S. 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 intend to apply for restorations of patent term for patents that issue from some of our currently owned or licensed patents or patent applications to add patent life beyond their current expiration dates, depending on the expected length of the clinical trials, the eligibility of the product and other factors involved in the filing of the relevant NDA.

Market exclusivity provisions under the FDCA can also delay the submission or the approval of certain applications. The FDCA provides a five-year period of non-patent marketing exclusivity within the United States to NDAs for products containing chemical entities never previously approved by the FDA alone or in combination. A new chemical entity means a drug that contains no active moiety that has been approved by the FDA in any application submitted under Section 505(b) of the FDCA. An active moiety is the molecule or ion responsible for the action of the drug substance. During the exclusivity period, the FDA may not accept for review an abbreviated new drug application ("ANDA"), or a Section 505(b) (2) NDA submitted by another company for another version of such drug where the applicant does not own or have a legal right of reference to all the data required for approval. This exclusivity provision does not prevent the submission or approval of another full Section 505(b)(1) NDA, but such an NDA applicant would be required to conduct its own preclinical and adequate, well-controlled clinical trials to demonstrate safety and effectiveness. The FDCA also provides three years of marketing exclusivity for an NDA, Section 505(b)(2) NDA or supplement to an existing NDA if new clinical investigations, other than bioavailability studies, that were conducted or sponsored by the applicant are deemed by the FDA to be essential to the approval of the application. Such clinical trials may, for example, support new indications, dosages, routes of administration or strengths of an existing drug, or for a new use. This exclusivity, which is sometimes referred to as clinical investigation exclusivity, prevents the FDA from approving an application under a Section 505(b)(2) NDA or an ANDA for the same conditions of use associated with the new clinical investigations before the expiration of three years from the date of approval. Such three-year exclusivity, however, would not prevent the approval of another application if the applicant submits a Section 505(b)(1) NDA and has conducted its own adequate, well-controlled clinical trials demonstrating safety and efficacy, nor would it prevent approval of an ANDA or a Section 505(b)(2) NDA product that did not incorporate the exclusivity-protected aspects of the approved drug product. Under the BPCIA, an application for a biosimilar product may not be submitted to the FDA until four years following the date that the reference product was first licensed by the FDA. In addition, the approval of a biosimilar product may not be made effective by the FDA until 12 years from the date on which the reference product was first licensed. During this 12-year period of exclusivity, another company may still market a competing version of the reference product if the FDA approves a full BLA for the competing product containing that applicant's own preclinical data and data from adequate and well-controlled clinical trials to demonstrate the safety, purity and potency of its product. The BPCIA also created certain exclusivity periods for biosimilars approved as interchangeable products.

Pediatric exclusivity is another type of exclusivity in the United States. Pediatric exclusivity, if granted, provides an additional six months of exclusivity to any existing exclusivity (*e.g*., three- or five-year exclusivity) or patent protection for a drug. This six-month exclusivity, which runs from the end of other exclusivity or patent protection, may be granted based on the voluntary completion of a pediatric trial in accordance with an FDA-issued "Written Request" for such a trial.

Orange Book Listing

In seeking approval for a drug through an NDA, applicants are required to list with the FDA each patent whose claims cover the applicant's product or a method of using the product. Upon approval of a drug, each of the patents listed in the application for the drug is then published in the FDA's Approved Drug Products with Therapeutic Equivalence Evaluations, commonly known as the Orange Book. Drugs listed in the Orange Book can, in turn, be cited by potential competitors in support of approval of an ANDA or an application covered by Section 505(b)(2) of the FDCA. An ANDA provides for marketing of a drug product that has the same active ingredients, generally in the same strengths and dosage form, as the listed drug and has been shown through PK testing to be bioequivalent to the listed drug. Drugs approved in this way are commonly referred to as "generic equivalents" to the listed drug, and can often be substituted by pharmacists under prescriptions written for the original listed drug. Other than the requirement for bioequivalence testing, ANDA applicants are generally not required to conduct, or submit results of, preclinical studies or clinical tests to prove the safety or effectiveness of their drug product. Section 505(b)(2) applications provide for marketing of a drug product that may have the same active ingredients as the listed drug and contains full safety and effectiveness data as an NDA, but at least some of this information comes from studies not conducted by or for the applicant. This alternate regulatory pathway enables the applicant to rely, in part, on the FDA's findings of safety and efficacy for an existing product, or published literature, in support of its application. The FDA may then approve the new drug candidate for all or some of the labeled indications for which the referenced product has been approved, as well as for any new indication sought by the 505(b)(2) applicant.

The ANDA or Section 505(b)(2) applicant is required to certify to the FDA concerning any patents listed for the approved product in the FDA's Orange Book. Specifically, the applicant must certify that: (i) the required patent information has not been filed; (ii) the listed patent has expired; (iii) the listed patent has not expired but will expire on a particular date and approval is sought after patent expiration; or (iv) the listed patent is invalid or will not be infringed by the new product. The ANDA or Section 505(b)(2) applicant may also elect to submit a statement certifying that its proposed ANDA label does not contain, or carves out, any language regarding a patented method of use rather than certify to such listed method of use patent. If the applicant does not challenge the listed patents by filing a certification that the listed patent is invalid or will not be infringed by the new product, the ANDA or Section 505(b)(2) application will not be approved until all the listed patents claiming the referenced product have expired.

A certification that the new product will not infringe the already approved product's listed patents, or that such patents are invalid, is called a Paragraph IV certification. If the ANDA or Section 505(b)(2) applicant has provided a Paragraph IV certification to the FDA, the applicant must also send notice of the Paragraph IV certification to the NDA and patent holders once the ANDA or Section 505(b)(2) application has been accepted for filing by the FDA. The NDA and patent holders may then initiate a patent infringement lawsuit in response to the notice of the Paragraph IV certification. The filing of a patent infringement lawsuit within 45 days of the receipt of a Paragraph IV certification automatically prevents the FDA from approving the ANDA or Section 505(b)(2) application until the earliest of 30 months, expiration of the patent, settlement of the lawsuit, and a decision in the infringement case that is favorable to the ANDA or Section 505(b)(2) applicant. This prohibition is generally referred to as the 30-month stay. Thus, approval of an ANDA or 505(b)(2) NDA could be delayed for a significant period of time depending on the patent certification the applicant makes and the reference drug sponsor's decision to initiate patent litigation.

The ANDA or Section 505(b)(2) application also will not be approved until any applicable non-patent exclusivity listed in the Orange Book for the referenced product has expired.

Post-Approval Requirements

Any drugs for which we receive FDA approval will be subject to continuing regulation by the FDA, including, among other things, record-keeping requirements, reporting of adverse experiences with the product, providing the FDA with updated safety and efficacy information, product sampling and distribution requirements, and complying with FDA promotion and advertising requirements.

The FDA strictly regulates marketing, labeling, advertising, and promotion of products that are placed on the market. Drugs may be promoted only for the approved indications and in accordance with the provisions of the approved label. The FDA and other government agencies enforce the laws and regulations prohibiting the false or misleading promotion of drugs. The FDA also limits the promotion of product candidates prior to their approval. With limited exceptions, pre-approval promotion is prohibited under the FDA's regulations.

Further, manufacturers of drugs must continue to comply with cGMP requirements, which are extensive and require considerable time, resources and ongoing investment to ensure compliance. In addition, changes to the manufacturing process may 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 subject to further FDA review and approval. Drug manufacturers and other entities involved in the manufacturing and distribution of approved drugs, and those supplying products, ingredients, and components of them, are required to list their products and 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, applicable product tracking and tracing requirements, and other laws. The cGMP requirements apply to all stages of the manufacturing process, including the production, processing, sterilization, packaging, labeling, storage and shipment of the drug. Manufacturers must establish validated systems to ensure that products meet specifications and regulatory standards and test each product batch or lot prior to its release. We rely, and expect to continue to rely, on third parties for the production of clinical and commercial quantities of our product candidates. FDA and state inspections may identify compliance issues at the facilities of our contract manufacturers that may disrupt production or distribution or may require substantial resources to correct.

The FDA may withdraw a product approval if compliance with regulatory standards is not maintained or if problems occur after the product reaches the market. Later discovery of previously unknown problems with a product may result in restrictions on the product or even complete withdrawal of the product from the market. Further, the failure to maintain compliance with regulatory requirements may result in administrative or judicial actions, such as fines, untitled and warning letters, holds on clinical trials, product recalls or seizures, product detention or refusal to permit the import or export of products, refusal to approve pending applications or supplements, restrictions on marketing or manufacturing, consent decrees, injunctions or the imposition of civil or criminal penalties.

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

Foreign Regulation

In addition to regulations in the United States, we will be subject to a variety of foreign regulations governing clinical trials of our product candidates and commercial sales and distribution of any product for which we obtain regulatory approval outside of the United States. Whether or not we obtain FDA approval for a product, we must obtain approval of a product by the comparable regulatory authorities of foreign countries before we can commence marketing of the product in those countries. The approval process varies from country to country, and the time may be longer or shorter than that required for FDA approval. The requirements governing the conduct of clinical trials, product licensing, pricing and reimbursement vary greatly from country to country. As in the United States, post-approval regulatory requirements, such as those regarding product manufacture, marketing or distribution, would apply to any product that is approved outside the United States.

For example, in the European Union, we may submit applications for marketing authorizations either under a centralized, decentralized, or mutual recognition marketing authorization procedure. The centralized procedure provides for the grant of a single marketing authorization for a medicinal product by the European Commission on the basis of a positive opinion by the European Medicines Agency. A centralized marketing authorization is valid for all European Union member states and three of the four European Free Trade Association States (Iceland, Liechtenstein and Norway). The decentralized procedure and the mutual recognition procedure apply between European Union member states. The decentralized marketing authorization procedure involves the submission of an application for marketing authorization to the competent authority of all European Union member states in which the product is to be marketed. One national competent authority, selected by the applicant, assesses the application for marketing authorization. The competent authorities of the other European Union member states are subsequently required to grant marketing authorization for their territory on the basis of this assessment, except where grounds of potential serious risk to public health require this authorization to be refused. The mutual recognition procedure provides for mutual recognition of marketing authorizations delivered by the national competent authorities of European Union member states by the competent authorities of other European Union member states. The holder of a national marketing authorization may submit an application to the competent authority of a European Union member state requesting that this authority recognize the marketing authorization delivered by the competent authority of another European Union member state for the same medicinal product.

We are also subject to the U.K. Bribery Act, and other third country anti-corruption laws and regulations pertaining to our financial relationships with foreign government officials. The U.K. Bribery Act, which applies to any company incorporated or doing business in the UK, prohibits giving, offering, or promising bribes in the public and private sectors, bribing a foreign public official or private person, and failing to have adequate procedures to prevent bribery amongst employees and other agents. Penalties under the Bribery Act include potentially unlimited fines for companies and criminal sanctions for corporate officers under certain circumstances. Liability in relation to breaches of the U.K. Bribery Act is strict. This means that it is not necessary to demonstrate elements of a corrupt state of mind. However, a defense of having in place adequate procedures designed to prevent bribery is available.

Formulary Approvals and Third-Party Payer Coverage and Reimbursement

In both the United States and foreign markets, our ability to successfully commercialize our product candidates for which we receive regulatory approval, and to attract commercialization partners for our product candidates, depends in significant part on the availability of institutional formulary approvals and on adequate financial coverage and reimbursement from third-party payers, including, in the United States. These payers include the Centers for Medicare & Medicaid Services (“CMS”), the federal program that runs the Medicare program, and monitors the Medicaid programs offered by each state, as well as national and regional commercial plans. Medicare is a federally funded program managed by CMS through local Medicare Administrative Contractors that administer coverage and reimbursement for certain healthcare items and services furnished to the elderly, disabled and other individuals with certain conditions. Medicaid is an insurance program for certain categories of patients whose income and assets fall below state defined levels that is both federally and state funded and managed by each state. The federal government sets general guidelines for Medicaid and each state creates specific regulations that govern its individual program. Each government or commercial plan has its own process and standards for determining whether it will cover and reimburse a procedure or particular product and how much it will pay for that procedure or product. Commercial plans often rely on the lead of the governmental payers in rendering coverage and reimbursement determinations. Therefore, achieving favorable Medicare coverage and reimbursement is usually an essential component of successfully launching a new product. The competitive position of some of our products will depend, in part, upon the extent of coverage and adequate reimbursement for such products and for the procedures in which such products are used. Reimbursement can be subject to challenge, reduction or denial by government and other commercial plans.

A primary trend in the U.S. healthcare industry and elsewhere is cost containment. Government healthcare programs and other third-party payers are increasingly challenging the prices charged for medical products and services and examining the medical necessity and cost-effectiveness of medical products and services, in addition to their safety and efficacy, and have attempted to control costs by limiting coverage and the amount of reimbursement for particular medications. Increasingly, third-party payers are challenging the prices charged for medical products and requiring that drug companies provide them with predetermined discounts from list prices.

The Inflation Reduction Act of 2022 (the "IRA") contains substantial drug pricing reforms, including the establishment of a drug price negotiation program within the U.S. Department of Health and Human Services that would require manufacturers to charge a negotiated "maximum fair price" for certain selected drugs or pay an excise tax for noncompliance, the establishment of rebate payment requirements on manufacturers of certain drugs payable under Medicare Parts B and D to penalize price increases that outpace inflation, and requires manufacturers to provide discounts on Part D drugs. Substantial penalties can be assessed for noncompliance with the drug pricing provisions in the IRA. The IRA could have the effect of reducing the prices we can charge and reimbursement we receive for our products, if approved, thereby reducing our profitability, and could have a material adverse effect on our financial condition, results of operations, and growth prospects. The effects of the IRA on our business and the pharmaceutical industry in general is not yet known.

Payers also are increasingly changing the metrics for reimbursement rates, such as basing payment on average sales price, average manufacturer price, and wholesale acquisition cost. The existing data for reimbursement based on these metrics is relatively limited, although certain states have begun to survey acquisition cost data for the purpose of setting Medicaid reimbursement rates. CMS surveys and publishes retail community pharmacy acquisition cost information in the form of National Average Drug Acquisition Cost files to provide state Medicaid agencies with a basis of comparison for their own reimbursement and pricing methodologies and rates. It may be difficult to project the impact of these evolving reimbursement mechanics on the willingness of payers to cover any products.

If we successfully commercialize any of our products, we may participate in the Medicaid Drug Rebate Program. Participation is required for federal funds to be available for our products under Medicaid and Medicare Part B. Under the Medicaid Drug Rebate Program, we would be required to pay a quarterly rebate to each state Medicaid program for our covered outpatient drugs that are dispensed to Medicaid beneficiaries and paid for by a state Medicaid program as a condition of having federal funds being made available to the states for our drugs under Medicaid and Part B of the Medicare program.

Federal law requires that any company that participates in the Medicaid Drug Rebate Program also participate in the Public Health Service's 340B drug pricing program in order for federal funds to be available for the manufacturer's drugs under Medicaid and Medicare Part B. The 340B drug pricing program requires participating manufacturers to agree to charge statutorily-defined covered entities no more than the 340B "ceiling price" for the manufacturer's covered outpatient drugs. These 340B covered entities include a variety of community health clinics and other entities that receive health services grants from the Public Health Service, as well as hospitals that serve a disproportionate share of low-income patients.

Additionally, in order to be eligible to have its products paid for with federal funds under the Medicaid and Medicare Part B programs and purchased by certain federal agencies and grantees, a manufacturer also must participate in the Department of Veterans Affairs, Federal Supply Schedule ("FSS"), pricing program, established by Section 603 of the Veterans Health Care Act of 1992 ("VHCA"). Under this program, the manufacturer is obligated to make its innovator and single source products available for procurement on an FSS contract and charge a price to four federal agencies, Department of Veterans Affairs, Department of Defense ("DoD"), Public Health Service, and Coast Guard, that is no higher than the statutory Federal Ceiling Price. Moreover, pursuant to regulations issued by the DoD's TRICARE Management Activity, now the Defense Health Agency, to implement Section 703 of the National Defense Authorization Act for Fiscal Year 2008, manufacturers are required to provide rebates on utilization of their innovator and single source products that are dispensed to TRICARE beneficiaries by TRICARE network retail pharmacies. The formula for determining the rebate is established in the regulations and is based on the difference between the annual non-federal average manufacturer price and the Federal Ceiling Price (these price points are required to be calculated by us under the VHCA). The requirements under the 340B, FSS, and TRICARE programs could reduce the revenue we may generate from any products that are commercialized in the future.

There may be significant delays in obtaining coverage and reimbursement for newly approved drugs, and coverage may be more limited than the purposes for which the drug is approved by the FDA or comparable foreign regulatory authorities. Moreover, eligibility for coverage and reimbursement does not imply that a drug will be paid for in all cases or at a rate that covers costs, including research, development, manufacturing, sale and distribution. Interim reimbursement levels for new drugs, if applicable, may also not be sufficient to cover costs and may only be temporary. Reimbursement rates vary according to the use of the drug and the clinical setting in which it is used. Product reimbursement may also be incorporated into existing bundled payments for other services. Net prices for drugs may be reduced by mandatory discounts or rebates required by government healthcare programs or commercial payers and by any future relaxation of laws that presently restrict imports of drugs from countries where they may be sold at lower prices than in the United States. Limited coverage may impact the demand for, or the price of, any product candidate for which marketing approval is obtained. Third-party payers also may seek additional clinical evidence, including expensive pharmacoeconomic studies, beyond the data required to obtain marketing approval, demonstrating clinical benefits and value in specific patient populations, before covering our products for those patients. If reimbursement is available only for limited indications, we may not be able to successfully commercialize any product candidate for which we obtain marketing approval. Our inability to promptly obtain coverage and profitable reimbursement rates from both government-funded and commercial payers for any approved products that we develop could have a material adverse effect on our operating results, our ability to raise capital needed to commercialize products and our overall financial condition.

United States Healthcare Reform

The United States and many foreign jurisdictions have enacted or proposed legislative and regulatory changes affecting the healthcare system, including implementing cost-containment programs to limit the growth of government-paid healthcare costs, including price controls, restrictions on reimbursement and requirements for substitution of generic products for branded prescription drugs.

In the United States, the Patient Protection and Affordable Care Act, as amended by the Health Care and Education Affordability Reconciliation Act (collectively, the "Affordable Care Act"), was intended to broaden access to health insurance, reduce or constrain the growth of healthcare spending, enhance remedies against fraud and abuse, add transparency requirements for the healthcare and health insurance industries, impose new taxes and fees on the health industry, and impose additional health policy reforms.

Among the provisions of the Affordable Care Act that have been implemented since enactment and are of importance to the commercialization of our product and product candidates, if approved, are the following:

- an annual, nondeductible fee on any entity that manufactures, or imports specified branded prescription drugs or biologic agents;
- an increase in the statutory minimum rebates a manufacturer must pay under the Medicaid Drug Rebate Program;
- expansion of healthcare fraud and abuse laws, including the U.S. civil False Claims Act and the Anti-Kickback Statute, new government investigative powers, and enhanced penalties for noncompliance;
- a 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 a manufacturer's outpatient drugs to be covered under Medicare Part D;
- extension of manufacturers' Medicaid rebate liability to covered drugs dispensed to individuals who are enrolled in Medicaid managed care organizations;
- 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;
- expansion of eligibility criteria for Medicaid programs;
- expansion of the entities eligible for discounts under the Public Health Service pharmaceutical pricing program;

- requirements to report certain financial arrangements with physicians and teaching hospitals;
- a requirement to annually report certain information regarding drug samples that manufacturers and distributors provide to physicians; and
- a new Patient-Centered Outcomes Research Institute to oversee, identify priorities in, and conduct comparative clinical effectiveness research, along with funding for such research.

There have been significant ongoing judicial, administrative, executive and legislative efforts to modify or eliminate the Affordable Care Act. For example, the Tax Act enacted on December 22, 2017, repealed the shared responsibility payment for individuals who fail to maintain minimum essential coverage under section 5000A of the Internal Revenue Code, commonly referred to as the individual mandate. Other legislative changes have been proposed and adopted since passage of the Affordable Care Act. The Budget Control Act of 2011, among other things, created the Joint Select Committee on Deficit Reduction to recommend proposals in spending reductions to Congress. The Joint Select Committee did not achieve its targeted deficit reduction of an amount greater than $1.2 trillion for the fiscal years 2012 through 2021, triggering the legislation's automatic reductions to several government programs. These reductions included aggregate reductions to Medicare payments to healthcare providers of up to 2.0% per fiscal year, which went into effect in April 2013. Subsequent litigation extended the 2% reduction, on average, to 2030 unless additional Congressional action is taken. The Coronavirus Aid, Relief and Economic Security Act, which was designed to provide financial support and resources to individuals and businesses affected by the COVID-19 pandemic, suspended the 2% Medicare sequester from May 1, 2020 to March 31, 2022. From April through June 2022, a 1% reduction was in effect. As of July 2, 2022, the 2% cut resumed. The sequester will remain in place through 2030. On January 2, 2013, the American Taxpayer Relief Act was signed into law, which, among other things, reduced Medicare payments to several types of providers, including hospitals, imaging centers and cancer treatment centers, and increased the statute of limitations period for the government to recover overpayments to providers from three to five years.

The Affordable Care Act has also been subject to challenges in the courts. On December 14, 2018, a Texas U.S. District Court Judge ruled that the Affordable Care Act is unconstitutional in its entirety because the "individual mandate" was repealed by Congress. On December 18, 2019, the Fifth Circuit U.S. Court of Appeals held that the individual mandate is unconstitutional and remanded the case to the Texas District Court to reconsider its earlier invalidation of the entire Affordable Care Act. An appeal was taken to the U.S. Supreme Court. On June 17, 2021, the Supreme Court ruled that the plaintiffs lacked standing to challenge the law as they had not alleged personal injury traceable to the allegedly unlawful conduct. As a result, the Supreme Court did not rule on the constitutionality of the Affordable Care Act or any of its provisions.

Further changes to and under the Affordable Care Act remain possible but it is unknown what form any such changes or any law proposed to replace or revise the Affordable Care Act would take, and how or whether it may affect our business in the future. We expect that changes to the Affordable Care Act, the Medicare and Medicaid programs, changes allowing the federal government to directly negotiate drug prices and changes stemming from other healthcare reform measures, especially with regard to healthcare access, financing or other legislation in individual states, could have a material adverse effect on the healthcare industry. We also expect that the Affordable Care Act, as well as other healthcare reform measures that have and may be adopted in the future, may result in more rigorous coverage criteria and in additional downward pressure on the price that we receive for our product and product candidates, if approved. Any reduction in reimbursement from Medicare, Medicaid, or other government programs may result in a similar reduction in payments from private payers.

Other Healthcare Laws and Compliance Requirements

If we obtain FDA approval for any of our product candidates and begin commercializing those products in the United States, our activities will be subject to various federal and state fraud and abuse laws, including, without limitation, the federal Anti-Kickback Statute, the federal civil False Claims Act, and laws and regulations pertaining to limitations on and reporting of healthcare provider payments (physician sunshine laws). These laws and regulations are interpreted and enforced by various federal, state and local authorities including CMS, the Office of Inspector General for the U.S. Department of Health and Human Services, the U.S. Department of Justice, individual U.S. Attorney offices within the Department of Justice, and state and local governments. These laws include:

- the U.S. federal Anti-Kickback Statute, which prohibits, among other things, persons or entities from knowingly and willfully soliciting, offering, receiving or paying any remuneration, directly or indirectly, overtly or covertly, in cash or in kind, to induce or reward either the referral of an individual for, or the purchase, lease, order, or arranging for or recommending the purchase, lease or order of, any good or service, for which payment may be made, in whole or in part, under federal healthcare programs such as Medicare and Medicaid. A person or entity does not need to have actual knowledge of the statute or specific intent to violate it in order to have committed a violation;

- the U.S. civil False Claims Act (which can be enforced through "qui tam," or whistleblower actions, by private citizens on behalf of the federal government), prohibits any person from, among other things, knowingly presenting, or causing to be presented false or fraudulent claims for payment of government funds or knowingly making, using or causing to be made or used, a false record or statement material to an obligation to pay money to the government or knowingly and improperly avoiding, decreasing or concealing an obligation to pay money to the U.S. federal government;

- U.S. federal Health Insurance Portability and Accountability Act of 1996, which imposes criminal liability and amends provisions on the reporting, investigating, enforcement, and penalizing of civil liability for, among other things, knowingly and willfully executing, or attempting to execute, a scheme to defraud any healthcare benefit program, or knowingly and willfully falsifying, concealing or covering up a material fact or making any materially false statement, in connection with the delivery of, or payment for healthcare benefits, items or services by a healthcare benefit program, which includes both government and privately funded benefits programs; similar to the U.S. federal Anti-Kickback Statute, a person or entity does not need to have actual knowledge of the statute or specific intent to violate it in order to have committed a violation;

- state laws and regulations, including state anti-kickback and false claims laws, that may apply to our business practices, including but not limited to, research, distribution, sales and marketing arrangements and claims involving healthcare items or services reimbursed by any third-party payer, including private insurers; state laws that require pharmaceutical companies to comply with the pharmaceutical industry's voluntary compliance guidelines and the relevant compliance guidance promulgated by the U.S. federal government, or otherwise restrict payments that may be made to healthcare providers and other potential referral sources; and state laws and regulations that require drug manufacturers to file reports relating to pricing and marketing information, which requires tracking gifts and other remuneration and items of value provided to healthcare professionals and entities; and

- the Physician Payments Sunshine Act, implemented as the Open Payments program, and its implementing regulations, requires certain manufacturers of drugs, devices, biologics and medical supplies that are reimbursable under Medicare, Medicaid, or the Children's Health Insurance Program to report annually to CMS information related to certain payments made in the preceding calendar year

and other transfers of value to physicians and teaching hospitals, as well as ownership and investment interests held by physicians and their immediate family members; beginning in 2022, applicable manufacturers were required to report such information regarding payments and transfers of value provided, as well as ownership and investment interests held, during the previous year to physician assistants, nurse practitioners, clinical nurse specialists, certified nurse anesthetists, and certified nurse-midwives.

Violations of any of these laws or any other governmental regulations that may apply to us, may subject us to significant civil, criminal and administrative sanctions including penalties, damages, fines, imprisonment, and exclusion from government funded healthcare programs, such as Medicare and Medicaid, and/or adverse publicity.

Moreover, government entities and private litigants have asserted claims under state consumer protection statutes against pharmaceutical and medical device companies for alleged false or misleading statements in connection with the marketing, promotion and/or sale of pharmaceutical and medical device products, including state investigations and litigation by certain government entities regarding the marketing of opioid products.

Foreign Corrupt Practices Act

The Foreign Corrupt Practices Act ("FCPA") generally prohibits offering, promising, giving, or authorizing others to give anything of value, either directly or indirectly, to a non-U.S. government official in order to influence official action, or otherwise obtain or retain business. The FCPA also requires public companies to make and keep books and records that accurately and fairly reflect the transactions of the corporation and to devise and maintain an adequate system of internal accounting controls. Our industry is heavily regulated and therefore involves significant interaction with public officials, including officials of non-U.S. governments. Additionally, in many other countries, the health care providers who prescribe pharmaceuticals are employed by their government, and the purchasers of pharmaceuticals are government entities; therefore, our dealings with these prescribers and purchasers are subject to regulation under the FCPA. Recently, the SEC and Department of Justice have increased their FCPA enforcement activities with respect to pharmaceutical companies. Violations could result in fines, criminal sanctions against us, our officers, or our employees, the closing down of our facilities, requirements to obtain export licenses, cessation of business activities in sanctioned countries, implementation of compliance programs, and prohibitions on the conduct of our business.

Corporate Information

We were incorporated in Pennsylvania in 2019 and our office headquarters is located at 490 Lapp Road, Malvern, Pennsylvania 19355.

RISK FACTOR SUMMARY

The following summarizes the principal factors that make an investment in the Company speculative or risky, all of which are more fully described in the Risk Factors section below. This summary should be read in conjunction with the Risk Factors section contained herein, as well as the Risk Factors sections found in our Annual Reports on Form 10-K, subsequent reports on Form 10-Q, and our other public filings, and should not be relied upon as an exhaustive summary of the material risks facing our business. The occurrence of any of these risks could harm our business, financial condition, results of operations and/or growth prospects or cause our actual results to differ materially from those contained in forward-looking statements we have made and those we may make from time to time. You should consider all of the risk factors described in our public filings when evaluating our business.

Risks Relating to Our Financial Position and Need for Additional Capital

- If we are unable to meet the initial listing standards of Nasdaq by November 13, 2023, or otherwise regain compliance with the listing standards of Nasdaq, our common stock may become delisted, which could have a material adverse effect on the liquidity of our common stock and our ability to raise capital.
- We are required to use reasonable best efforts to solicit shareholder approval for the conversion of our Series X Preferred Stock and if we are unable to obtain such approval by December 29, 2023, then the holders of our Series X Preferred Stock may demand cash settlement upon attempted conversions. If the holders of our Series X Preferred Stock demand this cash-settlement right, we may not have sufficient capital to funds its operations.
- There is no guarantee that the Acquisition of TeraImmune by us will increase shareholder value or that TeraImmune will be successfully integrated into our operations or achieve its desired benefits.
- Our business has incurred significant losses since our inception, and we may continue to incur significant losses for the foreseeable future. We may never achieve profitability.
- We will need to raise additional funding to advance our product candidates, which may not be available on acceptable terms, or at all. Failure to obtain capital when needed may force us to delay, limit or terminate our product development efforts or other operations.
- We may be unsuccessful in obtaining a waiver or amendment to our Credit Agreement with respect to any existing events of default thereunder. The failure to obtain such a waiver or amendment, or otherwise cure any event of default under our Credit Agreement, could allow the lender to take enforcement action against the Company or certain of its assets, including accelerating the loans and other obligations under the Credit Agreement and taking any other remedial actions permitted under the Credit Agreement or applicable law, which would have a material adverse effect on our business, financial condition and results of operations and could require us to curtail or cease operations.
- Our shareholders may experience dilution in the future.

Risks Relating to the Business of TeraImmune

- Our platform has never been used to develop any approved, commercially viable products.
- Our Treg-based product candidates may cause undesirable side effects or have other properties that could halt their clinical development, prevent their regulatory approval, require expansion of trial size, limit their commercial potential or result in significant negative consequences.
- We currently store our T cells and research specimens at our research and development facilities and at the facilities of our clinical and/or manufacturing partners, and any damage or loss to our storage freezers and/or facilities from natural disasters or otherwise would cause delays in replacement, and our business could suffer.

- We will rely on third-party healthcare professionals to administer Tregs to patients, and our business could be harmed if these third parties administer these cells incorrectly.
- We believe we may require an updated and validated protocol for commercial-scale expansion and manufacturing of Tregs for conducting pivotal trials and for commercialization of our product candidates, if approved.
- We have not yet developed commercial-scale infrastructure for freezing and thawing large quantities of Tregs, which we believe will be required for the storage and distribution of our Tregs product candidates at commercial scale.
- Cell therapies are novel and present significant challenges.
- Public opinion and scrutiny of cell-based immunotherapy and genetic modification approaches may impact public perception of our company and Treg-based product candidates, or may adversely affect our ability to conduct our business and our business plans.
- We may rely on orphan drug status to develop and commercialize certain of our product candidates, but orphan drug designations may not confer marketing exclusivity or other expected commercial benefits and we may not be able to obtain orphan drug designations for our other product candidates.
- Because the target patient population for TI-168 and certain of our other potential product candidates is relatively small, we must achieve significant market share and maintain high per-patient prices for our products to achieve and maintain profitability.
- Cell-based therapies rely on the availability of specialty raw materials, which may not be available to us on acceptable terms or at all.

Risks Relating to Our Intellectual Property

- We own or license numerous pending patent applications and issued patents in the United States. If our pending patent applications fail to issue or if our issued patents are not sufficiently broad, expire or are successfully opposed, invalidated, or rendered unenforceable, our business will be adversely affected.
- The validity, scope and enforceability of any patents that cover our current or future product candidates can be challenged by third parties.
- If we are unable to maintain our licensed agreements with third parties, our business may be materially harmed.
- Third-party claims or litigation alleging infringement of patents or other proprietary rights may delay or prevent the development and commercialization of our product candidates.
- We may become involved in lawsuits to protect or enforce our patents, the patents of our licensors or our other intellectual property rights, which could be expensive, time consuming and unsuccessful.
- We may be subject to claims challenging the inventorship or ownership of our patents and other intellectual property.

Risks Relating to Ownership of Our Common Stock

- Pursuant to the terms of the Agreement and Plan of Merger, dated June 29, 2023, by and among the Company, Bounce Merger Sub I, Inc., Bounce Merger Sub II, LLC and TeraImmune, Inc. (the "**Merger Agreement**"), we are required to use reasonable best efforts to recommend that our shareholders approve the conversion of all outstanding shares of our Series X Preferred Stock into shares of our common stock. We cannot guarantee that our shareholders will approve this matter, and if they fail to do so, we may be required to settle their shares of Series X Preferred Stock for cash at a price per share equal to the as-converted fair value of such shares of Series X Preferred Stock and our operations may be materially harmed.

- Our stock price could be volatile as holders of our Series X Preferred Stock become able to convert their shares to common stock and sell these shares in the open market.

- Nasdaq may delist our common stock from its exchange, which could limit your ability to make transactions in our securities and subject us to additional trading restrictions.

- Our stock price has been and may continue to be volatile, and the value of an investment in our common stock may decline.

- The issuance or sale of shares of our common stock could depress the trading price of our common stock.

Risks Relating to the Reverse Stock Split

- We cannot assure you that we will meet the conditions of the Staff's Hearing Decision, even if the proposed Reverse Stock Split is approved.

- We cannot assure you that the proposed Reverse Stock Split will increase the price of the common stock.

- The proposed Reverse Stock Split may decrease the liquidity of the common stock and result in higher transaction costs.

RISK FACTORS

Risks Relating to Our Financial Position and Need for Additional Capital

If we are unable to meet the initial listing standards of Nasdaq by November 13, 2023, or otherwise regain compliance with the listing standards of Nasdaq, our common stock may become delisted, which could have a material adverse effect on the liquidity of our common stock and our ability to raise capital.

The listing standards of the Nasdaq Stock Market LLC provide, among other things, that a company, in order to qualify for continued listing, must (i) maintain shareholders' equity of at least $2,500,000 pursuant to Nasdaq Listing Rule 5550(b)(1) ("**Rule 5550(b)(1**)") and (ii) maintain a minimum bid price of at least $1.00 per share pursuant to Nasdaq Listing Rule 5550(a)(2) ("**Rule 5550(a)(2)**").

On November 18, 2022, the Nasdaq Listing Qualifications Department ("**Staff**") informed us that we did not comply with Rule 5550(b)(1). The Staff granted our request for an extension until May 15, 2023, to comply with Rule 5550(b)(1). On May 17, 2023, we received a delist determination letter from the Staff advising us that the Staff had determined that we did not meet the terms of such extension. We requested an appeal of the Staff's determination and submitted a hearing request to the Nasdaq Hearings Panel ("**Panel**"), which request stayed any delisting action by the Staff at least until the hearing process concludes and any extension granted by the Panel expires.

On June 9, 2023, we received a deficiency letter from the Staff notifying us that we are not in compliance with Rule 5550(a)(2) and because we effected two reverse stock splits over the previous two-year period with a cumulative ratio of 250 shares or more to one, we are not eligible for any compliance period specified in Nasdaq Listing Rule 5810(c)(3)(A). Our noncompliance with Rule 5550(a)(2) serves as an additional basis for delisting of our securities from the Nasdaq and the Panel will consider this matter in rendering a determination regarding the our continued listing on the Nasdaq. On June 29, 2023, our hearing with the Panel was held and we submitted our plan for compliance to the Panel. On July 24, 2023, we received a letter from the Staff ("**Hearing Decision**") notifying us of its decision to grant our request to continue our listing on Nasdaq on a conditional basis, subject to, among other things, our ability to demonstrate compliance with the Nasdaq initial listing requirements by or before November 13, 2023. There can be no assurance that we will meet the conditions set forth by the Staff in the Hearing Decision, or that we will be able to regain compliance with such applicable Nasdaq listing requirements.

Furthermore, we believe that our acquisition of TeraImmune will, upon shareholder approval of Proposal No. 1, be considered a "change of control" transaction under Nasdaq rules. As such, the Company must meet Nasdaq's initial listing requirements. Accordingly, the Company must meet all the requirements set forth in Nasdaq Listing Rule 5505(a) and at least one of the standards set forth in Nasdaq Listing Rule 5505(b).

The listing standards of Nasdaq Listing Rule 5505(a) require the Company to have, among other things:

- a minimum bid price that is greater than or equal to $4.00 per share;
- at least 1,000,000 unrestricted publicly held shares;
- at least 300 round-lot holders, and at least 50% of such round lot holders must each hold unrestricted securities with a market value of at least $2,500;
- at least three registered and active market makers; and
- a minimum average daily trading volume of 2,000 shares over the 30 trading day period prior to listing, with trading occurring on more than half of those 30 days, unless such security is listed on Nasdaq in connection with a firm commitment underwritten public offering of at least $4 million.

The Company must also satisfy at least one of the following Nasdaq Listing Rule 5505(b) requirements:

- shareholders' equity of at least $5 million, a market value of unrestricted publicly held shares of at least $15 million, and two years of operating history;
- a market value of listed securities of at least $50 million, shareholders' equity of at least $4 million, and a market value of unrestricted publicly held shares of at least $15 million; or
- net income from continuing operations of $750,000 in the most recently completed fiscal year or in two of the three most recently completed fiscal years, shareholders' equity of at least $4 million, and a market value of unrestricted publicly held shares of at least $5 million.

There is no assurance that we will be able to meet Nasdaq's initial listing requirements or comply with the requisite Nasdaq requirements to maintain our listing of common stock on Nasdaq. If Nasdaq delists our securities from trading on its exchange and we are not able to list our securities on Nasdaq or any other national securities exchange, we could face significant material adverse consequences, including:

- a limited availability of market quotations for our common stock;
- reduced liquidity for our common stock;
- a determination that our common stock is a "penny stock," which will require brokers trading in our common stock to adhere to more stringent rules and possibly result in a reduced level of trading activity in the secondary trading market for its securities;
- a limited amount of news and analyst coverage for us;
- a decreased ability to issue additional securities or obtain additional financing in the future; and
- the incurring of additional costs under state blue sky laws in connection with any sales of our securities.

If our common stock is delisted by Nasdaq, our common stock may be eligible to trade on an over-the-counter quotation system, such as the OTCQB Market, where an investor may find it more difficult to sell our stock or obtain accurate quotations as to the market value of our common stock. In the event our common stock is delisted from Nasdaq, we may not be able to list our common stock on another national securities exchange or obtain quotation on an over-the counter quotation system.

We are required to use reasonable best efforts to solicit shareholder approval for the conversion of our Series X Preferred Stock and if we are unable to obtain such approval by December 29, 2023 (six months from the closing date of the Acquisition), then the holders of our Series X Preferred Stock may demand cash settlement upon attempted conversions. If the holders of our Series X Preferred Stock demand this cash-settlement right, we may not have sufficient capital to fund our operations.

Pursuant to the Merger Agreement, we are required to hold a special meeting of shareholders for the purpose of obtaining shareholder approval to allow for the conversion of our Series X Preferred Stock into common stock in accordance with Nasdaq Listing Rule 5635(a). If such shareholder approval is not received, we are required to convene additional shareholder meetings every six months thereafter until such approval is obtained, which could result in substantial costs and be a distraction to management.

Moreover, if shareholders do not approve the conversion of our Series X Preferred Stock into common stock by December 29, 2023 (six months from the closing date of the Acquisition), then the holders of our Series X Preferred Stock will have the right, in lieu of the conversion of such shares of Series X Preferred Stock into common stock, to require us to repurchase their shares of Series X Preferred Stock at the then-current fair value of the underlying common stock (determined on an as-converted basis). Failure to receive shareholder approval of the Conversion Proposal within six months from the closing of the Acquisition would have a material adverse effect on our financial position, and we could be forced to seek additional funding, which may not be available on acceptable terms or at all, or reduce or eliminate certain clinical trials, programs and operating expenses, which would adversely affect our business prospects.

There is no guarantee that the Acquisition of TeraImmune by us will increase shareholder value or that TeraImmune will be successfully integrated into our operations or achieve its desired benefits.

On June 29, 2023, we completed the Acquisition of TeraImmune. We cannot guarantee our integration efforts as a result of the Acquisition and the related transactions will not impair shareholder value or otherwise adversely affect our business. The Acquisition poses significant integration challenges between our businesses and management teams that could result in management and business disruptions, any of which could harm our results of operation, business prospects, and impair the value of such Acquisition to our shareholders.

Our business has incurred significant losses since our inception, and we may continue to incur significant losses for the foreseeable future. We may never achieve profitability.

Our business has incurred operating losses due to costs incurred in connection with our research and development activities, general and administrative expenses, and commercialization expenses associated with our operations. Our net losses from continuing operations for the quarters ended March 31, 2023 and 2022 were $7.4 million and $8.2 million, respectively. As of March 31, 2023, we had an accumulated deficit of $179.5 million. We launched ANJESO, our first commercial product, in mid-2020, but we have not generated significant revenue from sales of ANJESO, and in December 2022, we announced the discontinuation of the sale of ANJESO and are evaluating commercial partnering options for the product, including divestiture. For the years ended December 31, 2022 and 2021, net product revenue was $1.3 million and $1.1 million, respectively, related to sales of ANJESO in the U.S. Our product candidate pipeline includes early-stage product candidates, including a T cell-based immunotherapy for the treatment of Hemophilia A with inhibitors, two novel neuromuscular blocking agents ("**NMBs**"), and a related proprietary chemical reversal agent. If our product candidates are not successfully developed and approved, we may never generate any new revenue. All of our product candidates will require the expenditure of substantial additional development time and resources before we would be able to apply for or receive regulatory approvals and begin realizing product sales. We expect to continue to incur losses for the foreseeable future, and we anticipate these losses will increase as we continue our development of, seek regulatory approval for, and potentially commercialize any of our product candidates, if approved, and seek to identify, assess, acquire, in-license, or develop additional product candidates. Our prior losses, combined with expected future losses, have had and will continue to have a negative effect on our shareholders' deficit and working capital.

We expect that it will be several years, if ever, before we have a commercialized product. We anticipate that our expenses will increase substantially if, and as, we:

- continue clinical development of TI-168, BX1000 and BX2000 and preclinical development of BX3000, which is currently being evaluated in preclinical studies intended to support an IND filing in the last quarter of 2023, and our other preclinical T cell-based immunotherapies;
- seek to discover and develop additional product candidates;
- seek regulatory approvals for any of our product candidates that successfully complete clinical trials;
- maintain, expand, protect, and enforce our intellectual property portfolio;
- acquire or in-license other product candidates and technologies; and
- increase our employee headcount and related expenses to support these activities.

Because of the numerous risks and uncertainties associated with pharmaceutical product development and commercialization, we are unable to predict the timing or amount of increased expenses, and when, or if, we will be able to generate revenue or achieve or maintain profitability.

We will need to raise additional funding to advance our product candidates, which may not be available on acceptable terms, or at all. Failure to obtain capital when needed may force us to delay, limit or terminate our product development efforts or other operations.

Developing and commercializing pharmaceutical products and cell therapies, including conducting preclinical studies and clinical trials and ramping up commercialization and manufacturing activities, is a very time-consuming, expensive, and uncertain process that takes years to complete. We expect our expenses to increase in connection with our ongoing activities, particularly as we conduct preclinical and clinical trials of, and seek regulatory and marketing approval for, our product candidates. Even if one or more of our product candidates is approved for commercial sale, we anticipate incurring significant costs associated with commercializing any approved product candidate.

Our research and development expenses increased from $0.69 million for the quarter ended March 31, 2022 to $2.9 million for the quarter ended March 31, 2023. As of March 31, 2023, we had cash, and cash equivalents of $3.8 million. In April 2023, we completed a public offering of shares of common stock, together with accompanying common stock purchase warrants, and received net proceeds of approximately $3.4 million. Based on available sources, we believe our existing cash and cash equivalents will be sufficient to fund our currently anticipated operating expenses and capital expenditures requirements into the third quarter of 2023.

Attempting to secure additional financing will divert our management from our day-to-day activities, which may impair or delay our ability to develop our product candidates. Raising funds in the current economic environment may present substantial challenges, and future financing may not be available in sufficient amounts or on acceptable terms, if at all. If we are unable to raise capital when needed or on reasonable terms, we may curtail, delay or discontinue our research or development programs or wind down our business. In addition, demands on our cash resources may change as a result of many factors currently unknown to us including, but not limited to, any unforeseen costs we may incur as a result of preclinical study or clinical trial delays due to the COVID-19 pandemic or other pandemics, epidemics or outbreaks of a contagious illness, and we may need to seek additional funds sooner than planned. If we are unable to obtain funding on a timely basis or at all, we may be required to significantly curtail or stop one or more of our research or development programs and could have a material adverse effect on our business, operating results and prospects.

We may be unsuccessful in obtaining a waiver or amendment to our Credit Agreement with respect to any existing events of default thereunder. The failure to obtain such a waiver or amendment, or otherwise cure any event of default under our Credit Agreement, could allow the lender to take enforcement action against the Company or certain of its assets, including accelerating the loans and other obligations under the Credit Agreement and taking any other remedial actions permitted under the Credit Agreement or applicable law, which would have a material adverse effect on our business, financial condition and results of operations and could require us to curtail or cease operations.

On May 29, 2020, we entered into that certain Credit Agreement, as amended (the "**Credit Agreement**") with Wilmington Trust, National Association, as administrative and collateral agent ("**Agent**"), and MAM Eagle Lender, LLC, as a lender ("**Lender**"). In connection with the Acquisition, we entered into a Forbearance Agreement, dated as of June 29, 2023, with Agent and Lender, as amended (the "**Forbearance Agreement**"), pursuant to which Agent and Lender agreed to forbear form exercising their rights and remedies with respect to certain events of default under the Credit Agreement until October 31, 2023.

There can be no assurance that Agent and Lender will provide us with a waiver of any events of default or agree to amend the Credit Agreement in a timely manner, or on acceptable terms, if at all to the extent any events of default have occurred and are continuing under the Credit Agreement. If we do not obtain an amendment or waiver of such events of default under the Credit Agreement, if any future events of default occur and are continuing or if the Lenders take the position that we have not complied with the terms of the Forbearance Agreement, there can be no assurance that the Lenders will not take action to collect payment of our debt or dispose of collateral securing the obligations under the Credit Agreement, which would harm our business, financial condition and results of operations and could require us to curtail or cease operations.

Our shareholders may experience dilution in the future.

In the future, our shareholders' percentage ownership in the company may be diluted because of equity issuances for acquisitions, capital market transactions or otherwise, including equity awards that we plan to grant to our directors, officers and employees. Such awards will have a dilutive effect on our earnings per share, which could adversely affect the market price of our common stock. From time to time, we expect to issue stock options or other share-based awards to employees under our employee benefits plans.

In addition, our Articles authorize us to issue, without the approval of our shareholders, one or more classes or series of preferred stock having such designation, powers, preferences and relative, participating, optional and other special rights, including preferences over our common stock with respect to dividends and distributions, as our board of directors may determine. The terms of one or more classes or series of preferred stock could dilute the voting power or reduce the value of our common stock. For example, we could grant the holders of preferred stock the right to elect some number of directors in all events or on the happening of specified events or the right to veto specified transactions. Similarly, the repurchase or redemption rights or liquidation preferences we could assign to holders of preferred stock could affect the residual value of the common stock.

Risks Relating to the Business of TeraImmune

Our TCR T cell platform has never been used to develop any approved, commercially viable products.

Our platform utilizing human regulatory T cells ("**Tregs**") for the treatment of autoimmune diseases has not yet yielded any approved commercially viable therapeutic products, and there can be no guarantee that our product development efforts using our platform will be fruitful. We could experience safety or efficacy issues in our future clinical trials which delay or prevent the further development of our Treg-based therapies, For example, our Treg-based therapies may be shown to yield a short duration of disease remission in patients with Hemophilia A, which may in turn effect the efficacy and commercial viability of our product candidates. We intend to invest in the development of our platform, and our failure to develop approved, commercially viable products would significantly limit our business and prospects and would adversely impact the market value of our common stock.

Our TCR Treg-based product candidates may cause undesirable side effects or have other properties that could halt their clinical development, prevent their regulatory approval, require expansion of trial size, limit their commercial potential or result in significant negative consequences.

Certain of our product candidates, including TI-168, involve genetically modified T cell-based immunotherapies. Undesirable or unacceptable side effects caused by our product candidates 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 U.S. Food and Drug Administration ("**FDA**") or other comparable foreign regulatory authorities. Results of our clinical trials could reveal a high and unacceptable severity and prevalence of side effects or unexpected characteristics. Approved autologous cell therapies and those under development have shown frequent rates of cytokine release syndrome and neurotoxicity, and adverse events have resulted in the death of patients. Certain of our product candidates, such as TI-168, undergo genetic engineering. As these are novel technologies, errors may occur or may not present until used in humans in the clinic, and could cause adverse events. While we believe that our manufacturing process yields Tregs that have an inherent safety profile that may limit adverse events, there can be no assurance that this is the case as these are novel therapeutics.

There is no guarantee that our Treg-based product candidates will not have side effects similar to those seen in other genetically modified cell therapies or that we will be able to prevent side effects from escalating to an unsafe level for our patients. Additionally, our initial product candidate is directed at treating patients with Hemophilia A. These patients are often have co-morbidities, and we expect they will receive our product candidate after the development of inhibitors preventing the use of other treatments for Hemophilia A, and these patients may be particularly susceptible to safety and toxicity risks. Further, these side effects may not be appropriately recognized or managed by the treating medical staff, as toxicities resulting from T cell therapy may be complicated and difficult to manage, which could result in patient death or other significant issues. Additionally, it can be difficult to determine if the serious adverse or unexpected side effects were caused by the product candidate or another factor.

Our Treg-based product candidate, including TI-168, have not been tested in humans in a clinical trial and we cannot guarantee that there will not be any unexpected side effects. Although we have completed preclinical studies designed to screen for toxicity caused by unintended off-target recognition in vivo by our novel binding domains, our product candidates may still cause unintended off-target recognition in patients. Additionally, our genetically modified T cells may still bind targets other than the target antigens. If significant unexpected binding or off-target binding occurs in normal tissue, our product candidates may target and kill the normal tissue in a patient, leading to serious and potentially fatal adverse events, undesirable side effects, toxicities or other unexpected characteristics. Detection of any significant unexpected or off-target binding may halt or delay any ongoing clinical trials for our product candidates and prevent or delay regulatory approval. While we have developed a preclinical screening process to identify cross-reactivity of our product candidates, we cannot be certain that this process will identify all potential off-target tissue that our product candidates may interact with. Any unexpected or off-target binding that impacts patient safety could materially impact our ability to advance our product candidates into clinical trials and ability to proceed to marketing approval and commercialization.

If serious adverse events or undesirable side effects arise, we could be required to suspend, delay, or halt our planned clinical trials and regulatory authorities could deny approval or require us to limit development of that product candidate to certain uses or subpopulations in which the undesirable side effects or other characteristics are less prevalent, less severe or more acceptable from a risk-benefit perspective. Undesirable side effects could also result in an expansion in the size of our clinical trials, increasing the expected costs and timeline of our clinical trials. Side effects that are observed during the trial, whether treatment related or not, could also affect patient recruitment for future trials or the ability of enrolled patients to complete the trial or result in potential product liability claims.

Further, if serious adverse events or undesirable side effects are identified during development or after approval and are determined to be attributed to any of our product candidates, we may be required to develop risk evaluation and mitigation strategies to ensure that the benefits of treatment with such product candidate outweigh the risks for each potential patient, which may include, among other things, a communication plan to health care practitioners, patient education, extensive patient monitoring or distribution systems and processes that are highly controlled, restrictive and more costly than what is typical for the industry.

Any of these occurrences may harm our business, financial condition and prospects significantly.

We currently store our T cells and research specimens at our research and development facilities and at the facilities of our clinical and/or manufacturing partners, and any damage or loss to our storage freezers and/or facilities from natural disasters or otherwise would cause delays in replacement, and our business could suffer.

Specimens are stored in our freezers at our research and development facilities. If these cells are damaged, including by the loss or malfunction of our freezers or our back-up power systems, as well as by damage from fire or other natural disasters, our development program could be delayed or terminated and our business could suffer. Loss of a significant supply would require manufacturing of additional vector which could cause us to incur significant additional expenses and liability.

We will rely on third-party healthcare professionals to administer our T cell-based product candidates to patients, and our business could be harmed if these third parties administer these cells incorrectly.

We will rely on the expertise of physicians, nurses and other associated medical personnel to administer our T cell-based product candidates to clinical trial patients. If these medical personnel are not properly trained to administer, or do not properly administer, our product candidates, the therapeutic effect of our product candidates may be diminished or the patient may suffer injury.

In addition, third-party medical personnel will have to be trained on proper methodology for thawing Tregs received from us. If this thawing is not performed correctly, the cells may become damaged and/or the patient may suffer injury. While we intend to provide training materials and other resources to these third-party medical personnel, the thawing of Tregs will occur outside our supervision and may not be administered properly. If, due to a third-party error, people believe that Tregs are ineffective or harmful, the desire to use Tregs may decline, which would negatively impact our business, reputation and prospects. We may also face significant liability even though we may not be responsible for the actions of these third parties.

We believe we may require an updated and validated protocol for commercial-scale expansion and manufacturing of our product candidates for conducting pivotal trials and for commercialization of our product candidates, if approved.

Future clinical trials that we conduct, as well as any potential commercialization of our product candidates when approved, will depend on the reliability, safety and efficacy of our protocols for manufacturing our product candidates at scale. Our efforts to scale up production of our product candidates in anticipation of future clinical trials or commercialization may reveal, an inability to overcome biology or may otherwise encounter challenges, including scrutiny from regulatory authorities. To the extent we encounter any such difficulties, our ability to conduct additional clinical trials or to scale for commercialization will be hindered or prevented, which would have an adverse effect on our business.

We have not yet developed commercial-scale infrastructure for freezing and thawing large quantities of Tregs, which we believe will be required for the storage and distribution of our T cell-based product candidates at commercial scale.

We have not demonstrated that Tregs can be frozen and thawed in large commercial-scale quantities without damage, in a cost-efficient manner and without degradation over long periods of time. We may encounter difficulties not only in developing freezing and thawing, but also in obtaining the necessary regulatory approvals for using such in treatment. If we cannot adequately demonstrate similarity of our frozen product to the unfrozen form to the satisfaction of the FDA, we could face substantial delays in our regulatory approvals. If we are unable to freeze Tregs for shipping purposes, our ability to promote adoption and standardization of our products, as well as achieve economies of scale by centralizing our production facility, will be limited. Even if we are able to successfully freeze and thaw Tregs in large quantities, we will still need to develop a cost-effective and reliable distribution and logistics network, which we may be unable to accomplish. For these and other reasons, we may not be able to commercialize Tregs on a large scale or in a cost-effective manner.

Cell therapies are novel and present significant challenges.

T cell-based product candidates represent a relatively new field for treatment of autoimmune disorders. Advancing this novel and personalized therapy creates significant challenges, including:

- obtaining regulatory approval, as the FDA and other regulatory authorities have limited experience with commercial development of cell therapies for autoimmune diseases;
- sourcing clinical and, if approved, commercial supplies for the materials used to manufacture and process our product candidates;
- developing a consistent and reliable process, while limiting contamination risks, for engineering and manufacturing T cells ex vivo and infusing the engineered cells into the patient;
- educating medical personnel regarding the potential safety benefits, as well as the challenges, of incorporating our product candidates into their treatment regimens;
- establishing sales and marketing capabilities upon obtaining any regulatory approval to gain market acceptance of a novel therapy; and
- the availability of coverage and adequate reimbursement from third-party payors for our novel and personalized therapy.

Public opinion and scrutiny of cell-based immunotherapy and genetic modification approaches may impact public perception of our company and T cell-based product candidates, or may adversely affect our ability to conduct our business and our business plans.

Our T cell-based product candidates utilize a relatively novel technology involving the genetic modification of human cells and utilization of those modified cells in humans. Public perception may be influenced by negative claims about our platform, or that of competitor's products and/or programs such as claims that cell-based immunotherapy is unsafe, unethical, expensive or immoral and, consequently, our approach may not gain the acceptance of the public or the medical community. Negative public reaction to cell-based immunotherapy in general and a recent increase in patient deaths and clinical holds by other companies could result in greater government regulation and stricter labeling requirements of cell-based immunotherapy products, including any of our product candidates, and could cause a decrease in the demand for any products we may develop. Negative public attitudes may adversely impact our ability to enroll patients in clinical trials. Moreover, our success will depend upon physicians specializing in the treatment of those diseases that our product candidates target prescribing, and their patients being willing to receive, treatments that involve the use of our product candidates in lieu of, or in addition to, existing treatments they are already familiar with and for which greater clinical data may be available. More restrictive government regulations or negative public opinion could have an adverse effect on our business or financial condition and may delay or impair the development and commercialization of our product candidates or demand for any products we may develop. Adverse events in our clinical trials, even if not ultimately attributable to our product candidates, and the resulting publicity could result in increased governmental regulation, unfavorable public perception, potential regulatory delays in the testing or approval of our potential product candidates, stricter labeling requirements for those product candidates that are approved and a decrease in demand for any such product candidates.

We may rely on orphan drug status to develop and commercialize certain of our product candidates, but orphan drug designations may not confer marketing exclusivity or other expected commercial benefits and we may not be able to obtain orphan drug designations for our other product candidates.

We may rely on orphan drug exclusivity for product candidates that we may develop. Orphan drug status confers seven years of marketing exclusivity in the United States under the Federal Food, Drug, and Cosmetic Act ("**FDCA**"), and up to ten years of marketing exclusivity in Europe for a particular product in a specified indication, subject to certain conditions. However, we may be unable to obtain orphan drug designations for any of our product candidates that we are currently developing or may pursue. Even if we do obtain orphan drug designations and are the first to obtain marketing approval of our product candidates for the applicable indications, we will not be able to rely on these designations to exclude other companies from manufacturing or selling biological products using the same principal molecular structural features for the same indication beyond these timeframes. Furthermore, any marketing exclusivity in Europe can be reduced from ten years to six years if the initial designation criteria have significantly changed since the market authorization of the orphan product.

For any product candidate for which we may be granted orphan drug designation in a particular indication, it is possible that another company also holding orphan drug designation for the same product candidate will receive marketing approval for the same indication before we do. If that were to happen, our applications for that indication may not be approved until the competing company's period of exclusivity expires. Even if we are the first to obtain marketing authorization for an orphan drug indication in the United States, there are circumstances under which a competing product may be approved for the same indication during the seven-year period of marketing exclusivity, such as if the later product is shown to be clinically superior to our orphan product, or if the later product is deemed a different product than ours. Further, the seven-year marketing exclusivity would not prevent competitors from obtaining approval of the same product candidate as ours for indications other than those in which we have been granted orphan drug designation, or for the use of other types of products in the same indications as our orphan product.

Because the target patient population for TI-168 and certain of our other potential product candidates is relatively small, we must achieve significant market share and maintain high per-patient prices for our products to achieve and maintain profitability.

Certain of our Treg-based product candidates, including TI-168, target diseases with relatively small patient populations. As a result, our per-patient prices must be relatively high in order to recover our development and manufacturing costs and achieve and maintain profitability. In addition, because the number of potential patients in each disease population is small, it is not only important to find patients who begin therapy to achieve significant market penetration of the product, but we also need to be able to maintain these patients on therapy for an extended period of time. Due to the expected costs of treatment for our Treg-based product candidates, we may be unable to maintain or obtain sufficient market share at a price high enough to justify our product development efforts and manufacturing expenses.

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

Our Treg-based product candidates require many specialty raw materials, some of which are manufactured by small companies with limited resources and experience to support a commercial therapeutic, or to deliver raw materials to our specifications. The suppliers may be ill-equipped to support the manufacturing of our product candidates, especially in non-routine circumstances like an FDA inspection or medical crisis, such as widespread contamination. We generally do not have dedicated supply contracts with many of our suppliers, and we may not be able to contract with them on acceptable terms, or at all. Further, some of our suppliers may not be able to scale-up as we move to clinical trials or commercialization. Accordingly, we may experience delays in receiving, or fail to secure entirely, key raw materials to support clinical or commercial manufacturing. Certain raw materials also require third-party testing, and some of the testing service companies may not have capacity or be able to conduct the testing that we request.

We also face competition for supplies from other Treg-focused companies. Such competition may make it difficult for us to secure raw materials or the testing of such materials on commercially reasonable terms or in a timely manner.

Some raw materials are currently available from a single supplier, or a small number of suppliers. We cannot be sure that these suppliers will remain in business 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. In addition, the lead time needed to establish a relationship with a new supplier can be lengthy, and we may experience delays in meeting demand in the event we must switch to a new supplier. The time and effort to qualify a new supplier, including to meet any regulatory requirements for such qualification, could result in additional costs, diversion of resources or reduced manufacturing yields, any of which would negatively impact our operating results. Further, we may be unable to enter into agreements with a new supplier on commercially reasonable terms, which could have a material adverse impact on our business.

Risks Relating to Our Intellectual Property

We own or license numerous pending patent applications and issued patents in the United States. If our pending patent applications fail to issue or if our issued patents are not sufficiently broad, expire or are successfully opposed, invalidated, or rendered unenforceable, our business will be adversely affected.

Our commercial success will depend in part on obtaining and maintaining patent protection for our product candidates, as well as successfully defending our current and future patents against third-party challenges. To protect our proprietary technology, we intend to rely on patents, and we may also rely on other intellectual property protections, including trade secrets, nondisclosure agreements and confidentiality provisions.

There can be no assurance that our pending patent applications will result in issued patents. The patent applications that we have filed and have not yet been granted may fail to result in issued patents in the United States or foreign countries. Even if the patents do successfully issue, third parties may challenge the patents or the inventorship thereof, which can lead to an issued patent being found invalid, unenforceable or can otherwise alter the ownership of the patents.

The issuance of any patent is not a certainty. Unless and until our pending applications issue, their protective scope is impossible to determine. It is impossible to predict whether or how many of these applications will result in issued patents and patents that issue may be challenged in the courts or patent offices in the United States and abroad. Such challenges may result in loss of patent exclusivity or freedom to operate or in patent claims being narrowed, invalidated or held unenforceable, in whole or in part, which may limit our ability to prevent others from using or commercializing similar or identical technology and products, or limit the duration of the patent protection of our technology and products. In addition, upon expiration of a patent, we may be limited in our ability to prevent others from using or commercializing subject matter covered by the expired patents. As a result, our owned and licensed patent portfolio may not provide us with sufficient rights to exclude others from commercializing products similar or identical to ours. The patent position of biotechnology and pharmaceutical companies, including us, generally is highly uncertain, involves complex legal and factual questions and has in recent years been the subject of much litigation. In addition, the laws of foreign countries may not protect our rights to the same extent as the laws of the United States. For example, European patent law restricts the patentability of methods of treatment of the human body more than United States law does. 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 the first filing, or in some cases at all. Therefore, we cannot know with certainty whether we or our licensors were the first to make the inventions claimed in 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. As a result, the issuance, scope, validity, enforceability and commercial value of our patent rights are highly uncertain. In addition, we may not be aware of particular prior art publications that may have an impact on patentability or enforceability. Further, the examination process may require us or our licensors to narrow the claims for our pending patent applications due to, for example, such prior art publications, which may limit the scope of patent protection that may be obtained if these applications issue. Our pending and future patent applications may not result in patents being issued which protect our technology or products, in whole or in part, or which effectively prevent others from commercializing competitive technologies and products. Furthermore, our pending applications cannot be enforced against third parties practicing the technology claimed in such applications unless and until a patent issues from such applications. Because the issuance of a patent is not conclusive as to its inventorship, scope, validity or enforceability, issued patents that we own or have licensed from third parties may be challenged in the courts or patent offices in the U.S. and abroad. Such challenges may result in the loss of patent protection, the narrowing of claims in such patents, and/or the invalidity or unenforceability of such patents, 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 for our technology and products. Changes in either the patent laws or interpretation of the patent laws in the United States and other countries may diminish the value of patents or narrow the scope of patent protection.

Patent reform legislation could increase the uncertainties and costs surrounding the prosecution of patent applications and the enforcement or defense of issued patents. The Leahy Smith America Invents Act (the "**Leahy Smith Act**") enacted in September 2011, brought significant changes to the U.S. patent system. These include provisions that affect the way patent applications are prosecuted and may also affect patent litigation. The United States Patent Office continues to develop and implement new regulations and procedures to govern administration of the Leahy Smith Act, and many of the substantive changes to patent law associated with the Leahy Smith Act became effective on March 16, 2013. The Leahy Smith Act and its implementation could increase the uncertainties and costs surrounding the prosecution of our patent applications and the enforcement or defense of our issued patent, all of which could have a material adverse effect on our business and financial condition.

We exclusively license from Cornell University issued patents in the U.S. and other major foreign markets directed to BX1000 that expire in 2027, subject to any applicable disclaimer or extension, along with a pending PCT application directed to certain methods of using BX1000 that, if issued, would expire in 2041, subject to any applicable disclaimer or extension. We also exclusively license from Cornell University issued patents in the U.S. and other major foreign markets directed to BX2000 that expire in 2033, subject to any applicable disclaimer or extension, along with a pending PCT application directed to certain methods of using BX2000 that, if issued, would expire in 2041, subject to any applicable disclaimer or extension. We exclusively license from the National Institutes of Health ("**NIH**") issued U.S. patents covering methods of producing a population of cells having stable, regulatory T cells and cell culture compositions containing isolated human regulatory T cells, antibodies and an oligonucleotide that expire in 2033 subject to any applicable disclaimer or extensions. We also exclusively license from Henry M. Jackson Foundation for the Advancement of Military Medicine, Inc. ("**HJF**") issued patents in the U.S. and a pending European patent application relating to methods of producing and stabilizing T cell populations enriched for regulatory T cells and cell culture compositions that expire in 2034 subject to any applicable disclaimer or extension. We also exclusively license from HJF a family of pending U.S. and foreign patent applications directed to immunosuppressive induced regulatory T cells and methods of producing these cells which if issued would expire in 2041 subject to any applicable disclaimer or extensions. With respect to intranasal dexmedetomidine, we own issued patents in the U.S. and certain major foreign markets that expire in 2032, subject to any disclaimers or extensions.

If we are unable to obtain and maintain trade secret or patent protection for any of our current product candidates and future product candidates or if the scope of the patent protection obtained is not sufficiently broad, we may not be able to compete effectively in our markets.

We rely, and will continue to rely, upon a combination of patents, trademarks, trade secret protection and confidentiality agreements with employees, consultants, collaborators, advisors and other third parties to protect the intellectual property related to our brand, current and future drug development programs and product candidates. Our success depends in large part on our ability to obtain and maintain patent protection in the U.S. and other countries with respect to our current product candidates and any future product candidates and their uses. We seek to protect our proprietary position by filing patent applications in the U.S. and abroad in the licensed territory related to our current and future drug development programs and product candidates, successfully defending our intellectual property rights against third-party challenges and successfully enforcing our intellectual property rights to prevent third-party infringement. The patent prosecution process is expensive and time-consuming, and we may not be able to file and prosecute all necessary or desirable 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 before it is too late to obtain patent protection. We may choose not to seek patent protection for certain innovations or products and may choose not to pursue patent protection in certain jurisdictions and under the laws of certain jurisdictions, patents or other intellectual property rights may be unavailable or limited in scope and, in any event, any patent protection we obtain may be limited. We generally apply for patents in those countries in the licensed territory where we intend to make, have made, use, offer for sale or sell products and where we assess the risk of infringement to justify the cost of seeking patent protection. However, we do not seek protection in all countries where we intend to sell products and we may not accurately predict all the countries where patent protection would ultimately be desirable. If we fail to timely file a patent application in any such country or major market, we may be precluded from doing so at a later date. We may also make statements to regulatory authorities during the regulatory approval process that may be inconsistent with positions that have been taken during prosecution of our patents, which may result in such patents being narrowed, invalidated or held unenforceable.

The patent applications that we in-license in the U.S. or in other foreign countries may fail to result in issued patents with claims that protect our product candidates or result in patents that are narrowed, invalidated or held unenforceable following challenge in certain jurisdictions. We cannot guarantee any current or future patents will provide us with any meaningful protection or competitive advantage. There is no assurance that all of the potentially relevant prior art relating to our patents and patent applications has been found, which can prevent a patent from issuing from a pending patent application or be used to invalidate an issued patent. The examination process may require us to narrow our claims, which may limit the scope of any patent protection we obtain. Even if patents do successfully issue based on our patent applications and even if such patents cover our product candidates, uses of our product candidates or other aspects related to our product candidates, third parties may challenge their validity, ownership, enforceability or scope, which may result in such patents being narrowed, invalidated or held unenforceable or circumvented, any of which could limit our ability to prevent competitors and other third parties from developing and marketing similar products or limit the length of terms of patent protection we may have for our product candidates, if approved, and technologies. Other companies may also design around our patents. Third parties may have blocking patents that could prevent us from marketing our product candidates, if approved, or practicing our own patented technology. Further, if we encounter delays in regulatory approvals, the period of time during which we could market a product candidate while under patent protection could be reduced. If any of our patents expire or are challenged, invalidated, circumvented or otherwise limited by third parties prior to the commercialization of our product candidates and if we do not own or have exclusive rights to other enforceable patents protecting our product candidates, competitors and other third parties could market products that are substantially similar to ours and our business would suffer.

If the patent applications we hold or have in-licensed with respect to our development programs and our product candidates fail to issue, if their breadth or strength of protection is threatened or if they fail to provide meaningful exclusivity for our product candidate, TI-168, it could dissuade companies from collaborating with us to develop our product candidates and threaten our ability to commercialize future drugs. Any such outcome could have an adverse effect on our business. Our pending patent applications cannot be enforced against third parties practicing the technology claimed in such applications unless and until a patent issues from such application.

The patent position of biotechnology and pharmaceutical companies is generally highly uncertain, involves complex legal, scientific and factual questions, and has in recent years been the subject of much litigation. The standards that the U.S. Patent and Trademark Office ("**USPTO**") and its foreign counterparts use to grant patents are not always applied predictably or uniformly. In addition, the laws of foreign countries may not protect our rights to the same extent as the laws of the U.S. and many companies have encountered significant problems in protecting and defending such rights in foreign jurisdictions.

Patent reform legislation in the U.S. could increase those uncertainties and costs surrounding the prosecution of our patent applications and the enforcement or defense of our issued patents. For example, the Leahy Smith Act was signed into law in 2011 and includes a number of significant changes to U.S. patent law. These include provisions that affect the way patent applications are prosecuted, redefine prior art and provide more efficient and cost-effective avenues for competitors to challenge the validity of patents. 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 party review, and derivation proceedings. After March 2013, under the Leahy Smith Act, the U.S. transitioned to a first inventor to file system in which, assuming that the other statutory requirements 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.

Publications of discoveries in scientific literature often lag behind the actual discoveries and patent applications in the U.S. and other jurisdictions are typically not published until 18 months after filing, or in some cases not until a patent issues. Therefore, we cannot know with certainty whether we were the first to make the inventions claimed in our owned or licensed patents or pending patent applications or that we were the first to file for patent protection of such inventions. As a result, the issuance, scope, validity, enforceability and commercial value of our patent rights are highly uncertain. Our pending and future patent applications may not result in patents being issued which protect current product candidates or any future product candidates, in whole or in part, or which effectively prevent others from commercializing competitive products. Changes in either the patent laws or interpretation of the patent laws in the U.S. and other countries may diminish the value of our patents or narrow the scope of our patent protection.

Moreover, we may be subject to a third-party pre-issuance submission of prior art to the USPTO or become involved in opposition, derivation, reexamination inter partes review, post-grant review or interference 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 our patent rights, allow third parties to commercialize current product candidates or any future product candidates and compete directly with us without payment to us, or result in our inability to manufacture or commercialize products without infringing third-party patent rights. In addition, if the breadth or strength of protection provided by our patents and patent applications is threatened, it could dissuade companies from collaborating with us to license, develop or commercialize current product candidates or any future product candidates.

The issuance of a patent is not conclusive as to its inventorship, scope, validity or enforceability, and our owned and licensed patents may be challenged in the courts or patent offices, both in the U.S. and abroad. Such challenges may result in loss of exclusivity or in patent claims being narrowed, invalidated or held unenforceable, in whole or in part, which could limit our ability to stop others from using or commercializing similar or identical products or limit the duration of the patent protection of our products. Moreover, patents have a limited lifespan. In the U.S., if all maintenance fees are timely paid, the natural expiration of a patent is generally 20 years from its earliest U.S. non-provisional filing date. In certain instances, the patent term may be adjusted to add additional days to compensate for delays incurred by the USPTO in issuing the patent. Also, the patent term may be extended for a period of time to compensate for at least a portion of the time a product candidate was undergoing FDA regulatory review. However, the life of a patent, and the protection it affords, is limited. Without patent protection for current product candidates or any future product candidates, we may be open to competition from generic versions of such products. Given the amount of time required for the development, testing and regulatory review of new product candidates, patents protecting such candidates might expire before or shortly after such candidates are commercialized. As a result, our owned and licensed patent portfolio may not provide us with sufficient rights to exclude others from commercializing products similar or identical to ours.

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

Filing, prosecuting and defending patents on current product candidates or any future product candidates in all countries throughout the world would be prohibitively expensive and even in countries where we have sought protection for our intellectual property, such protection may be less extensive than that provided in the U.S. The requirements for patentability may differ in certain countries, particularly developing countries and the breadth of patent claims allowed can be inconsistent. In addition, the laws of some foreign countries do not protect patent rights to the same extent as federal laws in the U.S. Consequently, we may not be able to prevent third parties from practicing our inventions in all countries outside the U.S. or from selling or importing products made using our inventions in certain jurisdictions. Competitors may exploit our inventions in jurisdictions where we have not obtained patent protection to develop their own products and may also export otherwise infringing products to territories where we have patent protection but where enforcement is not as strong as that in the U.S. 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.

We do not have patent rights in certain foreign countries in which a market may exist. Moreover, in foreign jurisdictions where we may obtain patent rights, proceedings to enforce such rights could result in substantial costs and divert our efforts and attention from other aspects of our business, could put our patents at risk of being invalidated or interpreted narrowly and our patent applications at risk of not issuing. The legal systems of certain countries, particularly certain developing countries, do not favor the enforcement of patents, trade secrets and other intellectual property protection, particularly those relating to biotechnology products, which could make it difficult for us to stop the infringement of our patents or marketing of competing products in violation of our proprietary rights generally. Proceedings to enforce our patent rights in foreign jurisdictions, whether or not successful, could result in substantial costs and divert our efforts and attention from other aspects of our business, could put our patents at risk of being invalidated or interpreted narrowly, 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. Thus, we may not be able to stop a competitor from marketing and selling in foreign countries products and services that are the same as or similar to our products and services and our competitive position in the international market would be harmed.

Many countries, including E.U. countries have compulsory licensing laws under which a patent owner may be compelled under specified circumstances to grant licenses to third parties. In those countries, we may have limited remedies if patents are infringed or if we are compelled to grant a license to a third party, which could materially diminish the value of those patents. This could limit our potential revenue opportunities. Accordingly, our efforts to enforce our intellectual property rights around the world may be inadequate to obtain a significant commercial advantage from the intellectual property that we develop or license.

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

Patents have a limited lifespan. In the U.S., if all maintenance fees are timely paid, the natural expiration of a patent is generally 20 years from its earliest U.S. non-provisional filing date. In certain instances, the patent term may be adjusted to add additional days to compensate for delays incurred by the USPTO in issuing the patent. Also, the patent term may be extended for a period of time to compensate for at least a portion of the time a product candidate was undergoing FDA regulatory review. However, the life of a patent and the protection it affords is limited. Even if patents covering our product candidates are obtained, once the patent life has expired, we may be open to competition from competitive products, including generics or biosimilars. Given the amount of time required for the development, testing and regulatory review of any new product candidate, patents protecting such candidates might expire before or shortly after such candidates are commercialized. As a result, our owned and licensed patent portfolio may not provide us with sufficient rights to exclude others from commercializing products similar or identical to ours.

If we are not able to obtain patent term extension in the U.S. under the Hatch-Waxman Act and in foreign countries under similar legislation, thereby potentially extending the term of our marketing exclusivity for our current product candidates or future product candidates that we may identify, our business may be harmed.

Our commercial success will largely depend on our ability to obtain and maintain patent and other intellectual property rights in the U.S. and other countries with respect to our proprietary technology, product candidates and our target indications. Our issued patents directed to our various product and product candidates expire between 2024 to 2041. Given the amount of time required for the development, testing and regulatory review of new product candidates, patents protecting our product candidates might expire before or shortly after such candidates begin to be commercialized. We expect to seek extensions of patent terms in the United States and, if available, in other countries where we are prosecuting patents.

Depending upon the timing, duration and specifics of FDA marketing approval of our current product candidates or other product candidates that we may identify, one of the U.S. patents covering each of such product candidates or the use thereof may be eligible for up to five years of patent term extension under the Drug Price Competition and Patent Term Restoration Act of 1984 (the "**Hatch-Waxman Act**"). The Hatch-Waxman Act allows a maximum of one patent to be extended per FDA approved product as compensation for the patent term lost during the FDA premarket 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 and only claims covering such approved drug product, a method for using it or a method for manufacturing it may be extended. Patent term extension also may be available in certain foreign countries, including the E.U., upon regulatory approval of our product candidates, based on similar legislation. Nevertheless, we may not be granted patent term extension either in the U.S. or in any foreign country 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 term of extension, as well as the scope of patent protection during any such extension, afforded by the governmental authority could be less than we request.

If we are unable to obtain patent term extension or the term of any such extension is less than we request, the period during which we will have the right to exclusively market our product may be shortened and our competitors may obtain approval to market competing products sooner and our revenue could be reduced, possibly materially.

It is possible that we will not obtain patent term extension under the Hatch-Waxman Act for a U.S. patent covering our current product candidates or other product candidates that we may identify even where that patent is eligible for patent term extension or if we obtain such an extension, it may be for a shorter period than we had sought. Further, for patents we may later in-license or jointly own, we may not have the right to control patent prosecution, including filing with the USPTO a petition for patent term extension under the Hatch-Waxman Act. Thus, if one of these patents was eligible for patent term extension under the Hatch-Waxman Act, we might not be able to control whether a petition to obtain a patent term extension would be filed or obtained from the USPTO.

Generic competitors can challenge the U.S. patents protecting our product candidates by filing an ANDA or 505(b)(2) NDA for a generic or a modified version of our product candidates or seek abbreviated approval for biological products that are biosimilar to or interchangeable with biologic product candidates and negatively affect our competitive position.

Separate and apart from the protection provided under the U.S. patent laws, drug candidates may be subject to the provisions of the Hatch-Waxman Act, which may provide drug candidates with either a three- or five-year period of marketing exclusivity following receipt of FDA approval. The Hatch-Waxman Act prohibits the FDA from accepting the filing of an abbreviated new drug application ("**ANDA**") (for a generic product) or a new drug application ("**NDA**") under Section 505(b)(2) of the FDCA ("**Section 505(b)(2) NDA**") (for a modified version of the product) for three years for active drug ingredients previously approved by the FDA or for five years for active drug ingredients not previously approved by the FDA.

There is an exception, however, for newly approved molecules that allows competitors to challenge a patent beginning four years into the five-year exclusivity period by alleging that one or more of the patents listed in the FDA's list of approved drug products are invalid, unenforceable and/or not infringed and submitting an ANDA for a generic version of a drug candidate. This patent challenge is commonly known as a Paragraph IV certification. If we have an Orange Book listed patent and a third party submits a Paragraph IV certification to the FDA, a notice of the Paragraph IV certification must also be sent to us once the third party's ANDA is accepted for filing by the FDA. We may then initiate a patent infringement lawsuit within 45 days of receipt of the notice and we will be entitled to a 30 month stay running from the end of the 5-year new chemical entity ("**NCE**") exclusivity period. If we do not file a patent infringement lawsuit within the required 45-day period, the third party's ANDA or 505(b)(2) NDA will not be subject to the 30-month stay and the FDA could approve the ANDA or 505(b)(2) NDA after expiration of any applicable marketing exclusivity, such as the 5-year NCE exclusivity period or 3-year clinical investigation exclusivity. Within the past several years, the generic industry has aggressively pursued approvals of generic versions of innovator drugs at the earliest possible point in time.

If a generic company is able to successfully challenge the patents covering drug candidates or design around our patents and obtain FDA approval for an ANDA or 505(b)(2) NDA, the generic company may choose to launch a generic or modified version of our drug candidate. Any launch of a generic or modified version of our drug candidates prior to the expiration of patent protection will have a material adverse effect on our revenues and our results of operations.

Our product candidates for which we intend to seek approval as a biological product may face competition sooner than anticipated. In the U.S., the Biologics Price Competition and Innovation Act ("**BPCIA**") created an abbreviated approval pathway for biological products that are biosimilar to or interchangeable with an FDA-licensed reference biological product. New biologics, TI-168, may be entitled to regulatory exclusivity under the BPCIA. The BPCIA grants new biologics 12 years of FDA-granted exclusivity from the date of FDA's licensure of the biologic. Further, under the BPCIA, an application for a biosimilar product may not be submitted to the FDA until four years following the date that the reference product was first licensed by the FDA. During the period of exclusivity, however, another company may still market a competing version of the reference product if the FDA approves a full Biologics License Application ("**BLA**") for the competing product containing the sponsor's own clinical data from adequate and well controlled clinical trials to demonstrate the safety, purity and potency of their product. After the expiration of the exclusivity period, the FDA can approve a biosimilar product through an abbreviated approval process. The law is complex and is still being interpreted and implemented by the FDA. As a result, its ultimate impact, implementation and meaning are subject to uncertainty.

For biologics subject to approval by the FDA via a BLA, TI-168, the BPCIA provides a mechanism for one or more third parties to seek FDA approval to manufacture or sell a biosimilar or interchangeable versions of brand name biological products. Due to the large size and complexity of biological products as compared to small molecules, a biosimilar must be "highly similar" to the reference product with "no clinically meaningful differences between the two." The BPCIA, requires a formal pre-litigation process which includes the exchange of information between a biosimilar applicant and a reference biologic sponsor that includes the identification of relevant patents and each parties' basis for infringement and invalidity. After the exchange of this information, we may then initiate a lawsuit within 30 days to defend the patents identified in the exchange. If the biosimilar applicant successfully challenges the asserted patent claims it could result in the invalidation of or render unenforceable some or all of the relevant patent claims or result in a finding of non-infringement. Such litigation or other proceedings to enforce or defend intellectual property rights are often very complex in nature, may be very expensive and time-consuming, may divert our management's attention from our core business and may result in unfavorable results that could limit our ability to prevent third parties from competing with TI-168 or any future product candidates.

We believe that TI-168 should qualify for the 12-year period of exclusivity. However, there is a risk that this exclusivity could be shortened due to congressional action or otherwise, potentially creating the opportunity for generic competition sooner than anticipated. Other aspects of the BPCIA, some of which may impact the BPCIA exclusivity provisions, have also been the subject of litigation. Moreover, the extent to which a biosimilar, once approved, will be substituted for any one of our reference products in a way that is similar to traditional generic substitution for non-biological products is not yet clear, and will depend on a number of marketplace and regulatory factors that are still developing.

Outside of the United States we cannot be certain that any country's patent or trademark office will not implement new rules that could seriously affect how we draft, file, prosecute and maintain patents, trademarks and patent and trademark applications.

We cannot be certain that the patent or trademark offices of countries outside the United States will not implement new rules that increase costs for drafting, filing, prosecuting and maintaining patents, trademarks and patent and trademark applications or that any such new rules will not restrict our ability to file for patent or trademark protection. For example, we may elect not to seek patent protection in some jurisdictions or for some drug candidates in order to save costs. We may be forced to abandon or return the rights to specific patents due to a lack of financial resources.

For example, following the result of a referendum in 2016, the U.K. left the EU on January 31, 2020, commonly referred to as Brexit. The impact of the withdrawal of the U.K. from the EU will not be known for some time, which could lead to a period of uncertainty relating to our ability to obtain and maintain patents and trademarks in the U.K. In 2012, the European Patent Package ("**EU Patent Package**") regulations were passed with the goal of providing for a single pan-European Unitary Patent, and a new European Unified Patent Court ("**UPC**") for litigation of European patents. It is possible that implementation of the EU Patent Package will occur in the first half of 2023. If the EU Patent Package is ratified and in effect, all European patents, including those issued prior to ratification, would by default automatically fall under the jurisdiction of the UPC and allow for the possibility of obtaining pan-European injunctions. Under the EU Patent Package as currently proposed, once the UPC is established, patent holders are permitted to "opt out" of the UPC on a patent-by-patent basis during an initial seven year period after the EU Patent Package is ratified. Owners of traditional European patent applications who receive notice of grant after the EU Patent Package is ratified could either accept a Unitary Patent or validate the patent nationally and file an opt-out demand. The EU Patent Package may increase the uncertainties and costs surrounding the enforcement or defense of our issued European patents and pending applications. The full impact on future European patent filing strategy and the enforcement or defense of our issued European patents in member states and/or the UPC is not known.

The validity, scope and enforceability of any patents that cover our current or future product candidates can be challenged by third parties.

As an alternate path to FDA approval, particularly for modifications to drug products previously approved by the FDA, an applicant may submit a Section 505(b)(2) NDA. Section 505(b)(2) was enacted as part of the Hatch-Waxman Act and it permits approval of applications other than those for duplicate products and permits reliance for such approvals on literature or on the FDA's findings of safety and effectiveness of an approved drug product. To the extent that a Section 505(b)(2) NDA relies on clinical trials conducted for a previously approved drug product or the FDA's prior findings of safety and effectiveness for a previously approved drug product, the Section 505(b)(2) applicant must submit patent certifications in its application with respect to any patents for the reference product that are listed in the FDA's publication, Approved Drug Products with Therapeutic Equivalence Evaluations, commonly referred to as the Orange Book. Specifically, the applicant must certify for each listed patent that, in relevant part, (1) the required patent information has not been filed; (2) the listed patent has expired; (3) the listed patent has not expired but will expire on a particular date and approval is not sought until after patent expiration; or (4) the listed patent is invalid, unenforceable or will not be infringed by the proposed new product. A certification that the new product will not infringe the previously approved product's listed patent or that such patent is invalid or unenforceable is known as a Paragraph IV certification. If the applicant does not challenge one or more listed patents through a Paragraph IV certification, the FDA will not approve the Section 505(b)(2) NDA until all the listed patents claiming the referenced product have expired. Further, the FDA will also not approve a Section 505(b)(2) NDA until any non-patent exclusivity, such as, for example, five-year exclusivity for obtaining approval of a new chemical entity, three-year exclusivity for an approval based on new clinical trials, or pediatric exclusivity, listed in the Orange Book for the reference product, has expired. If the Section 505(b)(2) NDA applicant has provided a Paragraph IV certification to the FDA, the applicant must also send notice of the Paragraph IV certification to the owner of the reference product and relevant patent holders within 20 days after the Section 505(b)(2) NDA has been accepted for filing by the FDA. The NDA and patent holders may then initiate a patent infringement suit against the Section 505(b)(2) applicant. Under the FDCA, the filing of a patent infringement lawsuit within 45 days of receipt of the notification regarding a Paragraph IV certification automatically prevents the FDA from approving the Section 505(b)(2) NDA for 30 months, beginning on the date the patent holder receives notice, or until the patent expires or a court deems the patent unenforceable, invalid or not infringed, whichever is earlier. Even if a patent infringement claim is not brought within the 45-day period, a patent infringement claim may be brought under traditional patent law, but it does not invoke the 30-month stay. Moreover, in cases where a Section 505(b)(2) application containing a Paragraph IV certification is submitted after the fourth year of a previously approved drug's five-year exclusivity period, and the patent holder brings suit within 45 days of notice of certification, the 30-month period is automatically extended to prevent approval of the Section 505(b)(2) application until the date that is seven and one-half years after approval of the previously approved reference product. The court also has the ability to shorten or lengthen either the 30-month or the seven and one-half year period if either party is found not to be reasonably cooperating in expediting the litigation. Thus, the Section 505(b)(2) applicant may invest a significant amount of time and expense in the development of its product only to be subject to significant delay and patent litigation before its product may be commercialized. Alternatively, if the NDA applicant or relevant patent holder does not file a patent infringement lawsuit within the specified 45-day period, the FDA may approve the Section 505(b)(2) application at any time, assuming the application is otherwise approvable.

For biologics subject to approval by the FDA via a BLA, such as TI-168, the BPCIA provides a mechanism for one or more third parties to seek FDA approval to manufacture or sell a biosimilar or interchangeable versions of brand name biological products. Due to the large size and complexity of biological products as compared to small molecules, a biosimilar must be "highly similar" to the reference product with "no clinically meaningful differences between the two." The BPCIA, requires a formal pre-litigation process which includes the exchange of information between a biosimilar applicant and a reference biologic sponsor that includes the identification of relevant patents and each parties' basis for infringement and invalidity. After the exchange of this information, we may then initiate a lawsuit within 30 days to defend the patents identified in the exchange. If the biosimilar applicant successfully challenges the asserted patent claims it could result in the invalidation of or render unenforceable some or all of the relevant patent claims or result in a finding of non-infringement. Such litigation or other proceedings to enforce or defend intellectual property rights are often very complex in nature, may be very expensive and time-consuming, may divert our management's attention from our core business and may result in unfavorable results that could limit our ability to prevent third parties from competing with TI-168 or any future product candidates.

If we are unable to maintain our licensed agreements with third parties, our business may be materially harmed.

We have licensed certain intellectual property rights, including certain intellectual property rights covering our product candidates, from Cornell University, NIH and HJF. We are dependent on the Cornell University, NIH and HJF agreements for the development, manufacture and commercialization of our product candidates. If, for any reason, our licenses with Cornell University, NIH and/or HJF are terminated or we otherwise lose those rights, it could adversely affect our business. The Cornell University, NIH and HJF license agreements impose, and any future collaboration agreements or license agreements we enter into are likely to impose, various development, commercialization, funding, milestone payment, royalty, diligence, sublicensing, insurance, patent prosecution and enforcement or other obligations on us. If we breach any material obligations, or use the intellectual property licensed to us in an unauthorized manner, we may be required to pay damages and Cornell University, NIH and HJF, as the licensors, may have the right to terminate the license, which could result in us being unable to develop, manufacture and sell products that are covered by the licensed technology or having to negotiate new or reinstated licenses on less favorable terms or enable a competitor to gain access to the licensed technology. 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 product candidates, 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 third-party 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 as well as our partners; and
- the priority of invention of patented technology.

In addition, the agreement under which we currently license intellectual property from NIH and HJF is complex, and certain provisions in the agreement 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 an adverse effect on our business, financial condition, results of operations and business 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 successfully develop and commercialize such affected product candidates, which could have an adverse effect on our business, financial conditions, results of operations and business prospects.

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

Periodic maintenance fees on any issued patent are due to be paid to the USPTO and other foreign patent agencies in several stages over the lifetime of the patent. The USPTO and various foreign national or international patent agencies require compliance with a number of procedural, documentary, fee payment and other similar provisions during the patent application process and fee payment during the life of a patent. While an inadvertent lapse can in many cases be cured by payment of a late fee or by other means in accordance with the applicable rules, there are situations in which noncompliance can result in abandonment or lapse of the patent or patent application, resulting in partial or complete loss of patent rights in the relevant jurisdiction. Noncompliance events that could result in abandonment or lapse of patent rights include, but are not limited to, failure to timely file national and regional stage patent applications based on our international patent application, failure to respond to official actions within prescribed time limits, nonpayment of fees and failure to properly legalize and submit formal documents. If we or our licensors fail to maintain the patents and patent applications covering our current product candidates or any of our future product candidates, our competitors might be able to enter the market earlier than anticipated, which would have an adverse effect on our business.

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

A third party may hold intellectual property, including patent rights that are important or necessary to the development of any of our product candidates. It may be necessary for us to use the patented or proprietary technology of third parties to commercialize our current product candidates or any future product candidates, in which case we would be required to obtain a license from these third parties on commercially reasonable terms. Such a license may not be available, or it may not be available on commercially reasonable terms. Our business would be harmed if we are not able to obtain such a license on commercially reasonable terms or at all, or if a non-exclusive license is offered and our competitors gain access to the same technology.

The risks described elsewhere pertaining to our intellectual property rights also apply to the intellectual property rights that we in-license and any failure by us or our licensors to obtain, maintain, defend and enforce these rights could have an adverse effect on our business. In some cases, we may not have control over the prosecution, maintenance or enforcement of the patents that we license and may not have sufficient ability to provide input into the patent prosecution, maintenance and defense process with respect to such patents and our licensors may fail to take the steps that we believe are necessary or desirable in order to obtain, maintain, defend and enforce the licensed patents.

Third-party claims or litigation alleging infringement of patents or other proprietary rights may delay or prevent the development and commercialization of our product candidates.

Our commercial success depends in part on our ability to operate while avoiding infringement and other violations of the patents and proprietary rights of third parties. However, our research, development and commercialization activities may be subject to claims that we infringe or otherwise violate patents or other intellectual property rights owned or controlled by third parties. There is a substantial amount of litigation, both within and outside the U.S., involving patent and other intellectual property rights in the biotechnology and pharmaceutical industries, including patent infringement lawsuits, interferences, derivation and administrative law proceedings, inter partes review and post grant review before the USPTO, as well as oppositions and similar processes in foreign jurisdictions. Our competitors in both the U.S. and abroad, many of which have substantially greater resources and have made substantial investments in patent portfolios and competing technologies, may have applied for or obtained or may in the future apply for or obtain, patents that will prevent, limit or otherwise interfere with our ability to make, use and sell, if approved, our product candidate. Numerous U.S. and foreign issued patents and pending patent applications, which are owned by third parties, exist in the fields in which we and our collaborators are developing product candidates. As the biotechnology and pharmaceutical industries expand and more patents are issued and as we gain greater visibility and market exposure as a public company, the risk increases that our product candidates or other business activities may be subject to claims of infringement of the patent and other proprietary rights of third parties. Third parties may assert that we are infringing their patents or employing their proprietary technology without authorization.

There may be third-party patents or patent applications with claims to materials, formulations, methods of manufacture or methods for treatment related to the use or manufacture of our product candidates. 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 may infringe. In addition, third parties may obtain patents in the future and claim that use of our technologies infringes upon these patents. If any third-party patents were held by a court of competent jurisdiction to cover the manufacturing process of our product candidates, any molecules formed during the manufacturing process or any final product itself, the holders of any such patents may be able to block our ability to commercialize such product candidate unless we obtained a license under the applicable patents or until such patents expire. Similarly, if any third-party patent was to be held by a court of competent jurisdiction to cover aspects of our formulations, processes for manufacture or methods of use, including combination therapy, the holders of any such patent may be able to block our ability to develop and commercialize the applicable product candidate unless we obtained a license or until such patent expires. In either case, such a license may not be available on commercially reasonable terms or at all. In addition, we may be subject to claims that we are infringing other intellectual property rights, such as trademarks or copyrights, or misappropriating the trade secrets of others and to the extent that our employees, consultants or contractors use intellectual property or proprietary information owned by others in their work for us, disputes may arise as to the rights in related or resulting know-how and inventions.

Parties making claims against us may obtain injunctive or other equitable relief, which could effectively block our ability to further develop and commercialize our product candidates. Defending these claims, regardless of their merit, would involve substantial litigation expense and would be a substantial diversion of employee resources from our business. In the event of a successful infringement or other intellectual property claim against us, 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 or redesign our affected products, which may be impossible or require substantial time and monetary expenditure. We cannot predict whether any such license would be available at all or whether it would be available on commercially reasonable terms. Furthermore, even in the absence of litigation, we may need to obtain licenses from third parties to advance our research or allow commercialization of our product candidates. We may fail to obtain any of these licenses at a reasonable cost or on reasonable terms, if at all. In that event, we would be unable to further develop and commercialize our product candidates, which could harm our business significantly. Claims that we have misappropriated the confidential information or trade secrets of third parties could have a similar negative impact on our business.

Some of our competitors may be able to sustain the costs of complex intellectual property litigation more effectively than we can because they have substantially greater resources. In addition, intellectual property litigation, regardless of its outcome, may cause negative publicity, adversely impact prospective customers, cause product shipment delays or prohibit us from manufacturing, importing, marketing or otherwise commercializing our product candidates or any future product candidates. Any uncertainties resulting from the initiation and continuation of any litigation could have an adverse effect on our ability to raise additional funds or otherwise have an adverse effect on our business, results of operation, financial condition or cash flows.

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. There could also be public announcements of the results of hearings, motions or other interim proceedings or developments, which could have an adverse effect on the price of shares of our common stock. If securities analysts or investors perceive these results to be negative, it could have an adverse effect on the price of shares of our common stock. The occurrence of any of these events may have an adverse effect on our business, results of operation, financial condition or cash flows.

We cannot provide any assurances that third-party patents do not exist which might be enforced against our product candidates or any future product candidates, resulting in either an injunction prohibiting our sales or, with respect to our sales, an obligation on our part to pay royalties or other forms of compensation to third parties.

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

We cannot guarantee that any of our or our licensors' patent searches or analyses, including the identification of relevant patents, the scope of patent claims or the expiration of relevant patents are complete or thorough, nor can we be certain that we have identified each and every third-party patent and pending application in the U.S. and abroad that is or may be relevant to or necessary for the commercialization of our product candidates or any future product candidates in any jurisdiction. Patent applications in the U.S. and elsewhere are not published until approximately 18 months after the earliest filing for which priority is claimed, with such earliest filing date being commonly referred to as the priority date. In addition, U.S. patent applications filed before November 29, 2000 and certain U.S. patent applications filed after that date that will not be filed outside the U.S. remain confidential until patents issue. Therefore, patent applications covering our product candidates or any future product candidates could have been filed by others without our knowledge. Additionally, pending patent applications that have been published can, subject to certain limitations, be later amended in a manner that could cover our product candidates or any future product candidates, including the use thereof, provided such pending patent applications result in issued patents, our ability to develop and market our product candidates or any future product candidates can be adversely affected in jurisdictions where such patents issue.

The scope of a patent claim is determined by an interpretation of the law, the written disclosure in a patent and the patent's prosecution history. Our interpretation of the relevance or the scope of a patent or a pending application may be incorrect, which may negatively impact our ability to market our product candidate, if approved. We may incorrectly determine that our applicable product candidate is not covered by a third-party patent or may incorrectly predict whether a third-party's pending application will issue with claims of relevant scope. Our determination of the expiration date of any patent in the U.S. or abroad that we consider relevant may be incorrect, and our failure to identify and correctly interpret relevant patents may negatively impact our ability to develop and market our product candidates or any future product candidates, if approved.

If we fail to identify and correctly interpret relevant patents, we may be subject to infringement claims. We cannot guarantee that we will be able to successfully settle or otherwise resolve such infringement claims. If we fail in any such dispute, in addition to being forced to pay damages, we may be temporarily or permanently prohibited from commercializing any of our products that are held to be infringing. We might, if possible, also be forced to redesign products so that we no longer infringe the third-party intellectual property rights. Any of these events, even if we were ultimately to prevail, could require us to divert substantial financial and management resources that we would otherwise be able to devote to our business.

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

Competitors may infringe or otherwise violate our patents, the patents of our licensors or misappropriate or violate our other intellectual property rights. To counter infringement or unauthorized use, we may be required to file legal claims, which can be expensive and time-consuming. In addition, in an infringement or misappropriation proceeding, a court may decide that a patent or trade secret of ours or our licensors is not valid or is unenforceable or may refuse to stop the other party from using the technology at issue on the grounds that our patents do not cover the technology in question. The standards that courts use to interpret patents are not always applied predictably or uniformly and can change, particularly as new technologies develop. As a result, we cannot predict with certainty how much protection, if any, will be given to our patents if we attempt to enforce them and they are challenged in court. Further, even if we prevail against an infringer in U.S. district court, there is always the risk that the infringer will file an appeal and the district court judgment will be overturned at the appeals court and/or that an adverse decision will be issued by the appeals court relating to the validity or enforceability of our patents.

An adverse result in any litigation or defense proceeding could put one or more of our patents at risk of being invalidated or interpreted narrowly in a manner insufficient to achieve our business objectives or could put our patent applications at risk of not issuing. The initiation of a claim against a third party may also cause the third party to bring counter claims against us such as claims asserting that our patents are invalid or unenforceable. In patent litigation in the U.S., 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, non-enablement or lack of written description or statutory subject matter. Grounds for an unenforceability assertion could be an allegation that someone connected with prosecution of the patent withheld relevant material information from the USPTO or made a materially misleading statement during prosecution.

Third parties may also raise similar validity claims before the USPTO in post-grant proceedings such as ex parte reexaminations, inter partes review, or post-grant review, or oppositions or similar proceedings outside the U.S., in parallel with litigation or even outside the context of litigation. The outcome following legal assertions of invalidity and unenforceability is unpredictable. We cannot be certain that there is no invalidating prior art of which we and the patent examiner were unaware during prosecution. For patents and patent applications that we may in-license, we may have a limited right or no right to participate in the defense of any licensed patents against challenge by a third party. If a defendant were to prevail on a legal assertion of invalidity or unenforceability, we would lose at least part, and perhaps all, of any future patent protection on our current product candidates or any future product candidates. Such a loss of patent protection could harm our business.

We may not be able to detect or prevent, alone or with our licensors, misappropriation of our intellectual property rights, particularly in countries where the laws may not protect those rights as fully as in the U.S. Our business could be harmed if in litigation the prevailing party does not offer us a license on commercially reasonable terms. Any litigation or other proceedings to enforce our intellectual property rights may fail and even if successful, may result in substantial costs and distract our management and other employees.

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. There could also be public announcements of the results of hearings, motions or other interim proceedings or developments. If securities analysts or investors perceive these results to be negative, it could have an adverse effect on the price of shares of our common stock.

Because of the expense and uncertainty of litigation, we may not be in a position to enforce our intellectual property rights against third parties.

Because of the expense and uncertainty of litigation, we may conclude that even if a third party is infringing our issued patent, any patents that may be issued as a result of our pending or future patent applications or other intellectual property rights, the risk-adjusted cost of bringing and enforcing such a claim or action may be too high or not in the best interest of our company or our shareholders. In such cases, we may decide that the more prudent course of action is to simply monitor the situation or initiate or seek some other non-litigious action or solution.

Changes in the patent laws or trade secret laws in the U.S. or other countries or jurisdictions could diminish the value of patents and trade secrets in general, thereby impairing our ability to protect current product candidates or any of our future product candidates.

As is the case with other biopharmaceutical companies, our success is heavily dependent on intellectual property, particularly patents and trade secrets relating to our product candidates and any future product candidates. Obtaining and enforcing patents in the biopharmaceutical industry involves both technological and legal complexity and is therefore costly, time consuming and inherently uncertain. Changes in either the patent or trade secret laws or interpretation of the such laws in the U.S. or USPTO rules and regulations could increase the uncertainties and costs.

In addition, the U.S. federal government retains certain rights in inventions produced with its financial assistance under the Bayh-Dole Act of 1980 (the "**Bayh-Dole Act**"). Under the Bayh-Dole Act, the federal government retains a "nonexclusive, nontransferable, irrevocable, paid-up license" for its own benefit. The Bayh-Dole Act also provides federal agencies with "march-in rights." March-in rights allow the government, in specified circumstances, to require the contractor or successors in title to the patent to grant a "nonexclusive, partially exclusive or exclusive license" to a "responsible applicant or applicants." If the patent owner refuses to do so, the government may grant the license itself.

The U.S. Supreme Court has ruled on several patent cases in recent years, either narrowing the scope of patent protection available in certain circumstances or weakening the rights of patent owners in certain situations. Depending on future actions by the U.S. Congress, the U.S. courts, the USPTO and the relevant law-making bodies in other countries, the laws and regulations governing patents and trade secrets could change in unpredictable ways that would weaken our ability to obtain new patents or to enforce our existing patents and patents that we might obtain in the future or the protection of our trade secrets.

Similarly, changes in patent law and regulations and trade secret laws in other countries or jurisdictions or changes in the governmental bodies that enforce them or changes in how the relevant governmental authority enforces such laws or regulations may weaken our ability to obtain new patents or to enforce patents that we have licensed or that we may obtain in the future. We cannot predict future changes in the interpretation of patent and trade secret laws or changes to patent or trade secret laws that might be enacted into law by U.S. and foreign legislative bodies. Those changes may materially affect our patents or patent applications and trade secrets and our ability to obtain additional patent protection in the future.

If we are unable to protect the confidentiality of our trade secrets and other proprietary information, including as a result of our reliance on third parties, our business and competitive position could be harmed.

In addition to seeking patents for our product candidate, we also rely on trade secrets, including unpatented know-how, technology and other proprietary information, to maintain our competitive position. We seek to protect our proprietary technology in part by entering into confidentiality agreements and, if applicable, material transfer agreements, consulting agreements or other similar agreements with our advisors, employees, third-party contractors and consultants prior to beginning research or disclosing proprietary information. Despite these efforts and the contractual provisions employed when working with third parties, the need to share trade secrets and other confidential information due to our reliance on third parties, increases the risk that such trade secrets become known by our competitors, are inadvertently incorporated into the technology of others or are disclosed or used in violation of these agreements. Any disclosure, either intentional or unintentional, by our employees, the employees of third parties with whom we share our facilities or third-party consultants and vendors that we engage to perform research, clinical trials or manufacturing activities or misappropriation by third parties (such as through a cybersecurity breach) of our trade secrets or proprietary information could enable competitors to duplicate or surpass our technological achievements, thus eroding our competitive position in our market.

Monitoring unauthorized uses and disclosures of our intellectual property is difficult and we do not know whether the steps we have taken to protect our intellectual property will be effective. In addition, we may not be able to obtain adequate remedies for any such breaches. Enforcing a claim that a party illegally disclosed or misappropriated a trade secret is difficult, expensive and time consuming and the outcome is unpredictable. In addition, some courts inside and outside the U.S. are less willing or unwilling to protect trade secrets. Further, our key employees, consultants, suppliers or other individuals with access to our proprietary technology and know-how may incorporate that technology and know-how into projects and inventions developed independently or with third parties. As a result, disputes may arise regarding the ownership of the proprietary rights to such technology or know-how and any such dispute may not be resolved in our favor. If any of our trade secrets were to be lawfully obtained or independently developed by a competitor, we would have no right to prevent them or those to whom they communicate it from using that technology or information to compete with us. If any of our trade secrets or other proprietary information were to be disclosed to or independently developed by a competitor, our competitive position could be harmed.

We may be subject to claims that our licensors, employees, consultants, independent contractors or we have wrongfully used or disclosed confidential information of their former employers or other third parties.

We do and may employ individuals who were previously employed at universities or other biotechnology or pharmaceutical companies, including our licensors, competitors or potential competitors. Although we seek to protect our ownership of intellectual property rights by ensuring that our agreements with our employees, consultants, collaborators, independent contractors and other third parties with whom we do business include provisions requiring such parties to assign rights in inventions to us and to not use the knowhow or confidential information of their former employer or other third parties, we may be subject to claims that we or our employees, consultants, collaborators or independent contractors have inadvertently or otherwise used or disclosed know-how or confidential information of their former employers or other third parties. Litigation may be necessary to defend against these claims. There is no guarantee of success in defending these claims, and if we fail in defending any such claims, in addition to paying monetary damages, we may lose valuable intellectual property rights or personnel, which could result in customers seeking other sources for the technology, or in ceasing from doing business with us. Such intellectual property rights could be awarded to a third party, and we could be required to obtain a license from such third party to commercialize our technology or our product candidate. Such a license may not be available on commercially reasonable terms or at all. Even if we are successful, litigation could result in substantial cost and be a distraction to our management and other employees. Moreover, any such litigation or the threat thereof may adversely affect our reputation, our ability to form strategic alliances or sublicense our rights to collaborators, engage with scientific advisors or hire employees or consultants, each of which would have an adverse effect on our business, results of operations and financial condition.

We may be subject to claims challenging the inventorship or ownership 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 patents, 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 candidate. Litigation may be necessary to defend against these and other claims challenging inventorship or ownership of our owned or in-licensed patents, trade secrets or other intellectual property. In addition, while it is our policy to require our employees and contractors who may be involved in the development of intellectual property to execute agreements assigning such intellectual property to us, we may be unsuccessful in executing such an agreement with each party who in fact develops intellectual property that we regard as our own. Our and their assignment agreements may not be self-executing or may be breached and we may be forced to bring claims against third parties or defend claims they may bring against us to determine the ownership of what we regard as our intellectual property. If we or our licensors fail in defending any such claims, in addition to paying monetary damages, we may lose valuable personnel or intellectual property rights, such as exclusive ownership of, or right to use, intellectual property that is important to our product candidate. Even if we and our licensors are successful in prosecuting or 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 an adverse effect on our business, financial condition, results of operations and prospects. Intellectual property litigation could cause us to spend substantial resources and distract our personnel from their normal responsibilities and have an adverse effect on the success of our business. 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 technical and management 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 an adverse effect on the price of shares 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. Accordingly, despite our efforts, we may not be able to prevent third parties from infringing upon or misappropriating our intellectual property. In addition, the uncertainties associated with litigation could compromise our ability to raise the funds necessary to continue our clinical trials and internal research programs or in-license needed technology or any future product candidates. Uncertainties resulting from the initiation and continuation of patent litigation or other proceedings could compromise our ability to compete in the marketplace, including compromising our ability to raise the funds necessary to continue our clinical trials, continue our research programs, license necessary technology from third parties or enter into development collaborations that would help us commercialize our product candidates or any future product candidates, if approved.

We may not be successful in obtaining necessary intellectual property rights to future products through acquisitions and in-licenses.

We may seek to acquire or in-license additional product candidates or technologies to grow our product offerings and intellectual property portfolio. However, we may be unable to acquire or in-license intellectual property rights relating to, or necessary for, any such product candidates from third parties on commercially reasonable terms or at all. In that event, we may be unable to develop or commercialize such product candidates or technology. We may also be unable to identify product candidates or technology that we believe are an appropriate strategic fit for our company and protect intellectual property relating to, or necessary for, such product candidates and technology.

The in-licensing and acquisition of third-party intellectual property rights for product candidates is a competitive area and a number of more established companies are also pursuing strategies to in-license or acquire third-party intellectual property rights for products that we may consider attractive or necessary. These established companies may have a competitive advantage over us due to their size, cash resources and greater clinical development and commercialization capabilities. Furthermore, companies that perceive us to be a competitor may be unwilling to assign or license rights to us. If we are unable to successfully obtain rights to additional technologies or products, our business, financial condition, results of operations and prospects for growth could suffer.

In addition, we expect that competition for the in-licensing or acquisition of third-party intellectual property rights for product candidates and technologies that are attractive to us may increase in the future, which may mean fewer suitable opportunities for us as well as higher acquisition or licensing costs. We may be unable to in-license or acquire the third-party intellectual property rights for product candidates or technology on terms that would allow us to make an appropriate return on our investment.

Intellectual property rights do not necessarily address all potential threats to our competitive advantage.

Once granted, patents may remain open to invalidity challenges including opposition, interference, re-examination, post-grant review, inter partes review, nullification or derivation action in court or before patent offices or similar proceedings for a given period after allowance or grant, during which time third parties can raise objections against such granted patent. In the course of such proceedings, which may continue for a protracted period of time, the patent owner may be compelled to limit the scope of the allowed or granted claims thus challenged or may lose the allowed or granted claims altogether.

In addition, the degree of future protection afforded by our intellectual property rights is uncertain because intellectual property rights afford only limited protection, and may not adequately protect our business, provide a barrier to entry against our competitors or potential competitors, or permit us to maintain our competitive advantage. Moreover, if a third party has intellectual property rights that cover the practice of our technology, we may not be able to fully exercise or extract value from our intellectual property rights. The following examples are illustrative:

- others may be able to make formulations or compositions that are the same as or similar to our current product candidates or future product candidates but that are not covered by the claims of the patents that we own or have licensed;
- others may be able to make a product that is similar to our product candidates and not covered by the patents that we exclusively licensed and have the right to enforce;
- we, our licensor or any collaborators might not have been the first to make or reduce to practice the inventions covered by the issued patents or pending patent applications that we own or have exclusively licensed;

- we, our licensor or any collaborators might not have been the first to file patent applications covering certain of our or our licensor's inventions;
- others may independently develop similar or alternative technologies or duplicate any of our technologies without infringing or misappropriating our intellectual property rights;
- it is possible that our pending patent applications will not lead to issued patents;
- patents that we own or have exclusively licensed may not provide us with any competitive advantage or may be held invalid or unenforceable as a result of legal challenges;
- our competitors might conduct research and development activities in the U.S. and other countries that provide a safe harbor from patent infringement claims for certain research and development activities, as well as 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;
- third parties performing manufacturing or testing for us using our product candidates or technologies could use the intellectual property of others without obtaining a proper license;
- parties may assert an ownership interest in our intellectual property and, if successful, such disputes may preclude us from exercising exclusive rights over that intellectual property;
- we may not develop or in-license additional proprietary technologies that are patentable;
- we may not be able to obtain and maintain necessary licenses on commercially reasonable terms or at all; and
- the patents of others may have an adverse effect on our business.

Should any of these events occur, our business, financial condition, results of operations and business prospects could be adversely affected.

Risks Relating to Ownership of Our Common Stock

Pursuant to the terms of the Merger Agreement, we are required to use reasonable best efforts to recommend that our shareholders approve the conversion of all outstanding shares of our Series X Preferred Stock into shares of our common stock. We cannot guarantee that our shareholders will approve this matter, and if they fail to do so, we may be required to settle their shares of Series X Preferred Stock for cash at a price per share equal to the as-converted fair value and our operations may be materially harmed.

Under the terms of the Merger Agreement, we agreed to use reasonable best efforts to call and hold a meeting of our shareholders to obtain the requisite approval for the conversion of all outstanding shares of Series X Preferred Stock issued in the Acquisition into shares of our common stock, as required by the Nasdaq listing rules, within 90 days after the date of the Merger Agreement and, if such approval is not obtained at that meeting, to seek to obtain such approval at an annual or special shareholders meeting to be held at least every six months thereafter until such approval is obtained, which would be time-consuming and costly.

Additionally, if our shareholders do not timely approve the conversion of our Series X Preferred Stock, then the holders of our Series X Preferred Stock may be entitled to require us to redeem their shares of Series X Preferred Stock for cash at a price per share equal to the then-current as-converted fair value (as such term is defined in the Series X Certificate of Designation) of the Series X Preferred Stock. As described in the Series X Certificate of Designation, the fair value of the Series X Preferred Stock is the last reported closing stock price of our Common Stock on Nasdaq on the trading day immediately prior to the date on which the notice of conversion is delivered. If we are forced to redeem a significant amount of shares of Series X Preferred Stock for cash as described above, such cash settlement could materially affect our results of operations, including raising a substantial doubt about our ability to continue as a going concern.

Our stock price could be volatile as holders of our Series X Preferred Stock become able to convert their shares to common stock and sell these shares in the open market.

Our stock price could be volatile as holders of our Series X Preferred Stock become able to convert their shares to common stock and sell these shares in the open market. As of the record date, we had approximately shares of common stock issued and outstanding and 27,089,719 shares of common stock potentially issuable upon conversion of all issued and outstanding shares of Series X Preferred Stock. If the shareholders approve the Conversion Proposal and shares of Preferred Stock are converted into common stock, as such shares of common stock become eligible for resale in the open market, our stock may experience higher volatility. If a significant number of shareholders seek to sell their shares upon becoming eligible to do so, our stock price may decline.

Nasdaq may delist our common stock from its exchange, which could limit your ability to make transactions in our securities and subject us to additional trading restrictions.

If our common stock is delisted from Nasdaq, our common stock would likely then trade only in the over-the-counter market. If our common stock were to trade on the over-the-counter market, selling our common stock could be more difficult because smaller quantities of shares would likely be bought and sold, transactions could be delayed, and we could face significant material adverse consequences, including: a limited availability of market quotations for our securities; reduced liquidity with respect to our securities; a determination that our shares are a "penny stock," which will require brokers trading in our securities to adhere to more stringent rules, possibly resulting in a reduced level of trading activity in the secondary trading market for our securities; a reduced amount of news and analyst coverage for our Company; and a decreased ability to issue additional securities or obtain additional financing in the future. These factors could result in lower prices and larger spreads in the bid and ask prices for our common stock and would substantially impair our ability to raise additional funds and could result in a loss of institutional investor interest and fewer development opportunities for us.

In addition to the foregoing, if our common stock is delisted from Nasdaq and it trades on the over-the-counter market, the application of the "penny stock" rules could adversely affect the market price of our common stock and increase the transaction costs to sell those shares. The SEC has adopted regulations which generally define a "penny stock" as an equity security that has a market price of less than $5.00 per share, subject to specific exemptions. If our common stock is delisted from Nasdaq and it trades on the over-the-counter market at a price of less than $5.00 per share, our common stock would be considered a penny stock. The SEC's penny stock rules require a broker-dealer, before a transaction in a penny stock not otherwise exempt from the rules, to deliver a standardized risk disclosure document that provides information about penny stocks and the risks in the penny stock market. The broker-dealer must also provide the customer with current bid and offer quotations for the penny stock, the compensation of the broker-dealer and the salesperson in the transaction, and monthly account statements showing the market value of each penny stock held in the customer's account. In addition, the penny stock rules generally require that before a transaction in a penny stock occurs, the broker-dealer must make a special written determination that the penny stock is a suitable investment for the purchaser and receive the purchaser's agreement to the transaction. If applicable in the future, these rules may restrict the ability of brokers-dealers to sell our common stock and may affect the ability of investors to sell their shares, until our common stock no longer is considered a penny stock.

Some provisions of our charter documents and Pennsylvania law may have anti-takeover effects that could discourage an acquisition of us by others, even if an acquisition would be beneficial to our shareholders and may prevent attempts by our shareholders to replace or remove our current management.

Provisions in our Second Amended and Restated Articles of Incorporation, as amended ("**Articles**"), and Second Amended and Restated Bylaws ("**Bylaws**") could make it more difficult for a third-party to acquire us or increase the cost of acquiring us, even if doing so would benefit our shareholders, or remove our current management. These include provisions that:

- divide our board of directors into three classes with staggered three-year terms;
- provide that a special meeting of shareholders may be called only by a majority of our board of directors, the chairman of our board of directors or our chief executive officer or president;
- establish advance notice procedures with respect to shareholder proposals to be brought before a shareholder meeting and the nomination of candidates for election as directors, other than nominations made by or at the direction of the board of directors or a committee of the board of director;
- provide that certain provisions of the Articles may only be amended with the affirmative vote of 66 2/3% of the holders of the outstanding shares of capital stock;
- provide that shareholders may only act at a duly organized meeting; and
- provide that members of our board of directors may be removed from office by our shareholders only for cause by the affirmative vote of 75% of the total voting power of all shares entitled to vote generally in the election of directors.

These provisions may frustrate or prevent any attempts by our shareholders to replace or remove our current management by making it more difficult for shareholders to replace members of our board of directors, who are responsible for appointing the members of our management. Because we are incorporated in Pennsylvania, we are governed by the provisions of the Pennsylvania Business Corporation Law of 1988, as amended ("**PBCL**"), which may discourage, delay or prevent someone from acquiring us or merging with us whether or not it is desired by or beneficial to our shareholders. Under Pennsylvania law, a corporation may not, in general, engage in a business combination with any holder of 20% or more of its capital stock unless the holder has held the stock for five years or, among other things, the board of directors has approved the transaction. Any provision of our Articles or Bylaws or Pennsylvania law that has the effect of delaying or deterring a change in control could limit the opportunity for our shareholders to receive a premium for their shares of our common stock and could also affect the price that some investors are willing to pay for our common stock.

Our Articles designate the state and federal courts located within the County of Philadelphia in the Commonwealth of Pennsylvania as the sole and exclusive forum for certain types of actions and proceedings that may be initiated by our shareholders, which could discourage lawsuits against us and our directors and officers.

Our Articles provide that, unless we consent in writing to the selection of an alternative forum, a state or federal court located within the County of Philadelphia in the Commonwealth of Pennsylvania will be the sole and exclusive forum for (i) any derivative action or proceeding brought on behalf of our company, (ii) any action asserting a claim of breach of a fiduciary duty owed by any of our directors, officers or other employees or our shareholders, (iii) any action asserting a claim arising pursuant to any provision of PBCL, or (iv) any action asserting a claim peculiar to the relationships among or between our company and our officers, directors and shareholders. Any person or entity purchasing or otherwise acquiring any interest in shares of our capital stock shall be deemed to have notice of and to have consented to the provisions of our Articles described above. This choice of forum provision may limit a shareholder's ability to bring a claim in a judicial forum that it finds favorable for the types of claims listed above, which may discourage lawsuits with respect to such claims. Alternatively, if a court were to find the choice of forum provision contained in our Bylaws to be inapplicable or unenforceable in an action, we may incur additional costs associated with resolving such action in other jurisdictions, which could harm our business, operating results and financial condition.

Our stock price has been and may continue to be volatile, and the value of an investment in our common stock may decline.

An active, liquid and orderly market for our common stock may not be sustained, which could depress the trading price of our common stock or cause it to continue to be highly volatile or subject to wide fluctuations. In the last 52 weeks, our common stock has traded as low as $0.5190 per share. Some of the factors that could negatively affect our share price or result in fluctuations in the price or trading volume of our common stock include, among other things:

- the commencement, enrollment, or results of our current and future preclinical studies and clinical trials, and the results of trials of our competitors or those of other companies in our market sector;
- regulatory approval of our product candidates, or limitations to specific label indications or patient populations for its use, or changes or delays in the regulatory review process;
- manufacturing, supply or distribution delays or shortages;
- our ability to identify and successfully acquire or in-license new product candidates on acceptable terms;
- FDA, state or international regulatory actions, including actions on regulatory applications any of our product candidates;
- legislative or regulatory changes;
- judicial pronouncements interpreting laws and regulations;
- changes in government programs;
- announcements of new products, services or technologies, commercial relationships, acquisitions or other events by us or our competitors;
- market conditions in the pharmaceutical and biotechnology sectors;
- fluctuations in stock market prices and trading volumes of similar companies;
- the volatility of capital markets and other adverse macroeconomic factors, including due to inflationary pressures, interest rate and currency rate fluctuations, economic slowdown or recession, banking instability, geopolitical tensions or the outbreak of hostilities or war;
- changes in accounting principles;
- litigation or public concern about the safety of our product candidates or similar product candidates;
- sales of large blocks of our common stock, including sales by our executive officers, directors and significant shareholders;
- our ability to obtain additional financing to advance our development operations;
- our announcement of financing transactions, including debt, convertible notes, warrant exchanges, etc.;
- our ability to regain and maintain compliance with the listing standard of Nasdaq;
- the continued negative effects of the COVID-19 pandemic on the global economy; and
- actions by institutional shareholders.

These broad market and industry factors may decrease the market price of our common stock, regardless of our actual operating performance. The stock market in general has from time-to-time experienced extreme price and volume fluctuations, including recently. In addition, in the past, following periods of volatility in the overall market and decreases in the market price of a company's securities, securities class action litigation has often been instituted against these companies. This litigation, if instituted against us, could result in substantial costs and a diversion of our management's attention and resources.

The issuance or sale of shares of our common stock could depress the trading price of our common stock.

If (i) we issue additional shares of our common stock or rights to acquire shares of our common stock in other future transactions, (ii) any of our existing shareholders sells a substantial amount of our common stock, or (iii) the market perceives that such issuances or sales may occur, then the trading price of our common stock may significantly decrease. In addition, our issuance of additional shares of common stock will dilute the ownership interests of our existing common shareholders.

We do not expect to pay any cash dividends for the foreseeable future.

We do not anticipate that we will pay any cash dividends to holders of our common stock in the foreseeable future. Instead, we plan to retain any earnings to maintain and expand our operations. Our ability to pay cash dividends is currently restricted by the terms of our credit facility with MAM Eagle Lender, LLC. Accordingly, investors must rely on sales of their common stock after price appreciation, which may never occur, as the only way to realize any return on their investment. As a result, investors seeking cash dividends should not purchase our common stock.

Risks Relating to the Reverse Stock Split

We cannot assure you that we will meet the conditions of the Staff's Hearing Decision, even if the proposed Reverse Stock Split is approved.

On July 24, 2023, we received the Hearing Decision from the Staff notifying us of its decision to grant our request to continue our listing on Nasdaq on a conditional basis, subject to, among other things, our ability to demonstrate compliance with the Nasdaq initial listing requirements by or before November 13, 2023. There can be no assurance that we will meet the conditions set forth by the Staff in the Hearing Decision or be able to comply with the Nasdaq initial listing requirements by November 13, 2023, or maintain compliance with other Nasdaq listing requirements, even if the Reverse Stock Split Proposal is approved by our shareholders. Further, even if the Reverse Stock Split Proposal is approved by our shareholders, there is uncertainty as to whether Pennsylvania courts would find the use of our Series C Preferred Stock to approve the Reverse Stock Split Proposal to be sufficient under Pennsylvania Law. The use of super-voting preferred stock, such as the Series C Preferred Stock, to approve an amendment to a company's articles of incorporation has not been validated by a Pennsylvania court to date and has been neither specifically prohibited by, nor provided for, in applicable statutes. If we are required to appeal any notification of delisting in the future, and such appeal is denied or if we fail to regain compliance with Nasdaq's continued listing standards during any future period granted by Nasdaq, our common stock will become subject to delisting from Nasdaq.

We cannot assure you that the proposed Reverse Stock Split will increase the price of the common stock.

We expect that the Reverse Stock Split will increase the market price of the common stock. However, the effect of the Reverse Stock Split on the market price of the common stock cannot be predicted with any certainty, and the history of reverse stock splits for other companies in our industry is varied, particularly since some investors may view a reverse stock split negatively. It is possible that the per share price of the common stock after the Reverse Stock Split will not increase in the same proportion as the reduction in the number of outstanding shares of common stock following the Reverse Stock Split, and the Reverse Stock Split may not result in a per share price that would attract investors who do not trade in lower priced stocks. In addition, we cannot assure you that the common stock will be more attractive to investors. Even if we implement the Reverse Stock Split, the market price of the common stock may decrease due to factors unrelated to the Reverse Stock Split, including our future performance. If the Reverse Stock Split is consummated and the trading price of our common stock declines, the percentage decline as an absolute number and as a percentage of our overall market capitalization may be greater than would occur in the absence of the Reverse Stock Split.

The proposed Reverse Stock Split may decrease the liquidity of the common stock and result in higher transaction costs.

The liquidity of the common stock may be negatively impacted by the Reverse Stock Split, given the reduced number of shares that would be outstanding after the Reverse Stock Split, particularly if the stock price does not increase as a result of the Reverse Stock Split. In addition, if the Reverse Stock Split is implemented, it may increase the number of our shareholders who own "odd lots" of fewer than 100 shares of common stock, which may be more difficult to sell. Brokerage commissions and other costs of transactions in odd lots are generally higher than the costs of transactions of more than 100 shares or of even multiples of 100 shares of common stock. Accordingly, the Reverse Stock Split may not achieve the desired results of increasing marketability of the common stock as described above.