

BELLICUM PHARMACEUTICALS, INC  
Form 10-K  
March 20, 2015

UNITED STATES

SECURITIES AND EXCHANGE COMMISSION

Washington, D.C. 20549

Form 10-K

(Mark One)

TANNUAL REPORT PURSUANT TO SECTION 13 OR 15(d) OF THE SECURITIES EXCHANGE ACT OF 1934  
For the fiscal year ended December 31, 2014

or

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

For the transition period from \_\_\_\_\_ to \_\_\_\_\_.

Commission file number 001-36783

Bellicum Pharmaceuticals, Inc.

(Exact name of registrant as specified in its charter)

Delaware 20-1450200  
(State or other jurisdiction of incorporation or organization) (I.R.S. Employer Identification No.)

2130 W. Holcombe Blvd., Ste. 800, Houston, TX 77030  
(Address of principal executive offices) (Zip Code)

(832) 384-1100

(Registrant's telephone number, including area code)

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

Title of each class	Name of each exchange on which registered
Common Stock, par value \$0.01 per share	The NASDAQ Global Market

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

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

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

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

Indicate by check mark whether the registrant has submitted electronically and posted on its corporate Website, if any, every Interactive Data File required to be submitted and posted pursuant to Rule 405 of Regulation S-T (§229.405 of this chapter) during the preceding 12 months (or for such shorter period that the registrant was required to submit and post such files). Yes  No

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

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

Large accelerated filer  Accelerated filer   
Non-accelerated filer  (Do not check if a smaller reporting company) Smaller reporting company

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

The registrant did not have a public float on the last business day of its most recently completed second fiscal quarter because there was no public market for the registrant's common equity as of such date.

The number of outstanding shares of the registrant's common stock as of March 15, 2015 was 26,378,474.

#### DOCUMENTS INCORPORATED BY REFERENCE

Portions of the registrant's definitive Proxy Statement for the registrant's 2015 Annual Meeting of Stockholders to be filed with the Securities and Exchange Commission within 120 days after registrant's fiscal year ended December 31, 2014 are incorporated by reference into Part III of this report.



BELLICUM PHARMACEUTICALS, INC.

Form 10-K

For the Fiscal Year Ended December 31, 2014

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## PART I

### Forward-Looking Statements

This Annual Report on Form 10-K, including the sections entitled “Business,” “Risk Factors” and “Management’s Discussion and Analysis of Financial Condition and Results of Operations,” may contain “forward-looking statements.” We may, in some cases, use words such as “anticipate,” “believe,” “could,” “estimate,” “expect,” “intend,” “may,” “plan,” “predict,” “project,” “should,” “will,” “would” or the negative of those terms, and similar expressions that convey uncertainty of future events or outcomes to identify these forward-looking statements. Any statements contained herein that are not statements of historical facts may be deemed to be forward-looking statements. Forward-looking statements in this Annual Report include, but are not limited to, statements about:

- the success, cost and timing of our product development activities and clinical trials;
- our ability to advance CID-based technologies, including CaspaCIDE, CIDE CAR, GoCAR-T and DeCIDE;
- our ability to obtain and maintain regulatory approval of BPX-501 and any other product candidates, and any related restrictions, limitations and/or warnings in the label of an approved product candidate;
- our ability to obtain funding for our operations, including funding necessary to complete further development and commercialization of our product candidates;
- the commercialization of our product candidates, if approved;
- our plans to research, develop and commercialize our product candidates;
- our ability to attract collaborators with development, regulatory and commercialization expertise;
- future agreements with third parties in connection with the commercialization of our product candidates and any other approved product;
- the size and growth potential of the markets for our product candidates, and our ability to serve those markets;
- the rate and degree of market acceptance of our product candidates;
- regulatory developments in the United States and foreign countries;
- our ability to contract with third-party suppliers and manufacturers and their ability to perform adequately;
- the success of competing therapies that are or may become available;
- our ability to attract and retain key scientific or management personnel;
- our ability to grow our organization and increase the size of our facilities to meet our anticipated growth;
- the accuracy of our estimates regarding expenses, future revenue, capital requirements and needs for additional financing;
- our expectations regarding the period during which we qualify as an emerging growth company under the Jumpstart Our Business Startups Act of 2012, or the JOBS Act;
- our use of the proceeds from our recently completed initial public offering; and
- our expectations regarding our ability to obtain and maintain intellectual property protection for our product candidates.

In some cases, you can identify these statements by terms such as “anticipate,” “believe,” “could,” “estimate,” “expects,” “intend,” “may,” “plan,” “potential,” “predict,” “project,” “should,” “will,” “would” or the negative of those terms, and similar expressions that convey uncertainty of future events or outcomes. These forward-looking statements reflect our management’s beliefs and views with respect to future events and are based on estimates and assumptions as of the filing date of this Annual Report and are subject to risks and uncertainties. We discuss many of these risks in greater detail under the heading “Risk Factors.” Moreover, we operate in a very competitive and rapidly changing environment. New risks emerge from time to time. It is not possible for our management to predict all risks, nor can we assess the impact of all factors on our business or the extent to which any factor, or combination of factors, may cause actual results to differ materially from those contained in any forward-looking statements we may make. Given these uncertainties, you should not place undue reliance on these forward-looking statements.

You should carefully read this Annual Report and the documents that we reference in this Annual Report completely and with the understanding that our actual future results may be materially different from what we expect. We qualify

all of the forward-looking statements in this Annual Report by these cautionary statements.

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Except as required by law, we undertake no obligation to update these forward-looking statements publicly, or to update the reasons that actual results could differ materially from those anticipated in any forward-looking statements, whether as a result of new information, future events or otherwise.

## ITEM 1. Business

### Overview

We are a clinical stage biopharmaceutical company focused on discovering and developing novel cellular immunotherapies for various forms of cancer, including both hematological cancers and solid tumors, as well as orphan inherited blood disorders. Cellular immunotherapy has the potential to transform medicine by harnessing immune cells, principally T cells, to attack and eliminate harmful diseased cells in the body. Unlike traditional small molecule and biologic therapies, which are predictably metabolized and eliminated from the body, cellular immunotherapies are unpredictable and uncontrollable. We are using our proprietary Chemical Induction of Dimerization, or CID, technology platform to engineer and then control components of the immune system in real time. By incorporating our CID platform, our product candidates may offer better safety and efficacy outcomes than are seen with current cellular immunotherapies.

We are developing next-generation product candidates in some of the most important areas of cellular immunotherapy, including hematopoietic stem cell transplantation, or HSCT, CAR T cell therapy, and dendritic cell vaccines. HSCT, also known as bone marrow transplantation, has for decades been curative for many patients with hematological cancers or orphan inherited blood disorders. However, application of HSCT is limited by graft-versus-host-disease, or GvHD, a condition in which the transplanted immune cells recognize the host cells as foreign and attack them. Since the transplanted cells can persist indefinitely, GvHD does not resolve by itself and is a major cause of transplant-related morbidity and mortality. CAR T cell therapy is an innovative approach in which a patient's T cells are genetically modified to carry chimeric antigen receptors, or CARs, which redirect the T cells against cancer cells. While high objective response rates have been reported in some hematological malignancies, serious and sometimes fatal toxicities have arisen in patients treated with CAR T cell therapies. These toxicities include instances in which the CAR T cells have caused high levels of cytokines due to over-activation, referred to as "cytokine release syndrome", frequent transient neurologic toxicities and cases in which they have attacked healthy organs instead of the targeted tumor, leading to death. In solid tumors, where the behavior of CAR T cells is particularly unpredictable and results have been inconsistent, researchers are developing enhanced CAR T cell approaches called "armored CARs" that raise even greater safety concerns. Lastly, despite the integral role that dendritic cells, specialized cells that are key regulators of the immune system that process and present antigens on the cell surface to T cells in order to activate the T cells, play in the immune system, they are difficult to activate appropriately and as a result their use has delivered only modest therapeutic benefit.

Our proprietary CID platform is designed to address these challenges. Events inside a cell are controlled by cascades of specialized signaling proteins. CID consists of molecular switches, modified forms of these signaling proteins, which are triggered inside the patient by infusion of a small molecule, rimiducid (AP1903), instead of by natural upstream signals. We include these molecular switches in the appropriate immune cells and deliver the cells to the patient in the manner of conventional cellular immunotherapy. We have developed two such switches: a "safety switch," designed to initiate programmed cell death, or apoptosis, of the immunotherapy cells, and an "activation switch," designed to stimulate activation and in some cases proliferation of the immunotherapy cells. Each of our technologies incorporates one of these switches, for enhanced, real time control of safety and efficacy:

- CaspaCIDE is our safety switch, incorporated into our HSCT and T-cell receptor, or TCR, product candidates, where it is inactive unless the patient experiences a serious side effect. In that event, rimiducid is administered to fully or partially eliminate the cells, with the goal of terminating or attenuating the therapy and resolving the serious side effect.

CIDeCAR consists of CAR T cells modified to include our CaspaCIDE safety switch and in which the CAR T cell incorporates the signaling domains of two proteins, MyD88 and CD40. Together, these form our proprietary dual co-stimulatory domain, MC, which is designed to activate T cells in the presence of cancer cells more potently than co-stimulatory molecules CD28 and 4-1BB, which are used in most investigational CAR T cell therapies.

Incorporation of CaspaCIDE in a CIDeCAR product candidate is intended to allow the enhanced potency of MC co-stimulation to be deployed safely in patients.

GoCAR-T consists of CAR T cells that are modified to include the proprietary dual co-stimulatory domain, MC. In contrast to CIDeCAR, MC is structured in GoCAR-T as a molecular switch, separate from the chimeric antigen receptor, which itself contains no co-stimulatory domains. GoCAR-T is designed to allow control of the activation and proliferation of the CAR T cells through the scheduled administration of a course of rimiducid infusions that may continue until the desired patient outcome is achieved. In the event of emergence of side effects, the level of activation of the GoCAR-T cells is designed to be attenuated by extending the interval between rimiducid doses and/or reducing the dosage per infusion.

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·DeCIDE consists of dendritic cells that are modified to include the same MC switch used in GoCAR-T. Upon exposure to rimiducid, dendritic cells containing DeCIDE become highly activated in a process that is less susceptible to being turned off by the immune system's natural inhibitory processes. By administering rimiducid after the patient has been vaccinated and the dendritic cells have had time to migrate to the draining lymph nodes, our DeCIDE product candidates are designed to be activated in a potent and long-lasting manner.

By incorporating our novel switch technologies, we are developing product candidates with the potential to elicit positive clinical outcomes and ultimately change the treatment paradigm in various areas of cellular immunotherapy. Our clinical product candidates; each of which is a combination product of genetically modified immune cells and rimiducid, are described below.

·BPX-501. We are developing a CaspaCIDE product candidate, BPX-501, as an adjunct T-cell therapy administered after allogeneic HSCT, using donor stem cells. In a typical allogeneic HSCT procedure, a patient receives a full complement of immune cells including both donor stem cells and donor T cells. T cells in the transplant often cause serious and potentially fatal side effects, such as GvHD. BPX-501 is designed to decrease the risk of including T cells with the transplant by enabling the elimination of donor T cells through the triggering of the CaspaCIDE safety switch upon emergence of GvHD. In a 10-patient Phase 1 clinical trial with CaspaCIDE modified T cells, conducted by an academic collaborator, four patients developed GvHD after donor T-cell infusion. A single dose of rimiducid rapidly eliminated over 90% of the modified T cells and resolved GvHD in all four patients without recurrence of GvHD. BPX-501 is currently being evaluated in multiple Phase 1/2 clinical trials in the United States and Europe to assess whether BPX-501 T cells from haplo-identical donors administered following HCST are safe and can help speed immune reconstitution. The initial top-line data from ongoing studies is expected by the end of 2015.

·BPX-201. We are developing a DeCIDE product candidate, BPX-201, as a dendritic cell cancer vaccine made from the patient's own white blood cells, designed to treat metastatic castrate-resistant prostate cancer or, mCRPC. It targets the prostate specific membrane antigen, or PSMA, and uses our DeCIDE activation switch technology. BPX-201 is currently being evaluated in an 18-patient Phase 1 clinical trial for mCRPC. We are evaluating opportunities for BPX-201 in combination with other cancer immunotherapies, such as checkpoint inhibitors, which are antibodies designed to block certain inhibitory receptors on the surface of T cells, and thus potentiate the T cells' ability to promote an immune response against cancer. We believe that the increased numbers of PSMA-specific T cells migrating to deposits of prostate cancer in the body that BPX-201 is designed to generate may serve as a substrate for checkpoint inhibitors, resulting in a synergistic, more potent anti-cancer immune response.

In addition, our preclinical product candidates are designed to overcome the current limitations of CAR-T and TCR therapies and include the following:

·BPX-401. We are developing a CIDECAR product candidate, BPX-401, as a next-generation CAR T cell therapy for hematological cancers that express the CD19 antigen. CD19 is an antigen expressed in many hematological cancers, including acute lymphocytic leukemia, or ALL, chronic lymphocytic leukemia, or CLL, and certain non-Hodgkin's lymphomas. We believe that, while the activity of CAR T cell therapy has been demonstrated in early-stage clinical trials by third party researchers in these indications, safety issues, such as cytokine release syndrome, a systemic inflammatory response that is produced by elevated levels of cytokines that are associated with T-cell activation and proliferation, remain a major concern, which may be addressed by BPX-401.

·BPX-601. We are developing a GoCAR-T product candidate, BPX-601, for solid tumors overexpressing the prostate stem cell antigen, or PSCA, such as some prostate, pancreatic, bladder, esophageal and gastric cancers. We have obtained positive proof-of-principle data in an animal pancreatic tumor model, which we believe validate BPX-601's activity and rimiducid's ability to modulate therapeutic effect.

·BPX-701. We are developing a CaspaCIDE TCR product candidate, BPX-701, in collaboration with Leiden University Medical Center, initially for the treatment of PRAME-expressing sarcomas and neuroblastomas. Based on in vitro studies, BPX-701 has demonstrated strong affinity to panels of cancer cells presenting PRAME peptides and low affinity to non-tumor cells. In other in vitro studies, rimiducid administration has shown the ability to eliminate BPX-701 cells.

We expect to file investigational new drug applications, or INDs, for BPX-701 by the end of 2015 and for BPX-401 and BPX-601 in 2016. Our IND-enabling activities for each of these preclinical product candidates, include

manufacturing key components and developing a robust process to produce cell products that comply with regulations of the U.S. Food and Drug Administration, or FDA, and other regulatory agencies. We have developed an efficient and scalable process to manufacture genetically modified T cells of high quality and purity. This process is being implemented by our third-party contract manufacturers to produce BPX-501 for our clinical trials. We expect to leverage our resources, capabilities and expertise for the manufacture of our CAR-T and TCR product candidates.

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## Recent Developments

On December 23, 2014, the closing of our initial public offering triggered an acceleration of the payment of \$15 million due to ARIAD Pharmaceuticals, Inc., or ARIAD, under our omnibus amendment agreement with ARIAD and our promissory note issued to ARIAD. As a result of such acceleration, on December 29, 2014, we paid to ARIAD an aggregate amount of \$35 million, which included an additional payment of \$20 million to extinguish the promissory note. In connection with the note payments and pursuant to the omnibus amendment agreement, ARIAD returned to us all of the 677,463 shares of our common stock then held by ARIAD.

## Cellular Immunotherapy

Cellular immunotherapy harnesses a patient's own immune cells to attack and eliminate harmful disease cells in the body. The immune system is the body's defense network. It consists of a number of cells and organs that, working together, recognize and respond to threats in the form of pathogens. T cells are a type of white blood cell that recognize pathogens and can target and eliminate them upon full activation through the addition of appropriate co-stimulatory signals.

Dendritic cells, another component of the immune system, are antigen-presenting cells found in skin and other tissues like the lining of the gut that can sense and respond to the environment. Dendritic cells engulf and process potential threats they encounter, presenting them as antigens to T cells and B cells to allow the body to mount an immune response.

The following three therapeutic applications of cellular immunotherapy have been the primary areas of research and development by research institutes and biopharmaceutical companies, given their promise of effectively treating patients suffering from severe and life-threatening diseases.

**HSCT.** HSCT is the transplantation of stem cells and other immune cells derived from bone marrow, peripheral blood or umbilical cord blood. The transplantation may be autologous, using the patient's own cells, or allogeneic, using a donor's cells. HSCT is often the only curative option for a wide range of treatment-refractory hematological cancers, such as ALL, acute myeloid leukemia, or AML, and chronic myeloid leukemia, or CML. HSCT is also used as a high-risk treatment for orphan inherited blood disorders, such as sickle cell disease, beta-thalassemia and certain immune disorders.

**Dendritic Cell Therapy.** Whereas HSCT and CAR T cells involve direct administration of T cells to the patient, dendritic cell therapies are designed to indirectly stimulate T cells already present in the patient. Given the important role of dendritic cells in initiating an immune response in the body, substantial research has been conducted to leverage the attributes of dendritic cells to treat cancer. Cancer vaccines are the most common form of dendritic cell-based therapy. These vaccines entail collecting certain monocytes, a type of white blood cell, from the patient's body, maturing them into dendritic cells, "loading" them ex vivo with the patient's cancer antigens, and sometimes modifying them in other ways to improve their potency, and then re-infusing the modified dendritic cells in the patient.

**Genetically Modified T-cell Therapy (CAR-T and TCR).** This approach entails collecting a patient's T cells, genetically modifying them ex vivo, or outside of the body, to incorporate specific receptors which target cancer cells and then re-infusing the modified T cells back into the patient. Two types of cancer-specific receptors are typically used, CARs that recognize whole antigens on the surface of cancer cells, and TCRs that bind to cancer-associated peptides, or fragments of proteins, from either inside or on the surface of the cancer cells. In early human clinical trials, CAR T cell therapy has demonstrated an unprecedented ability to achieve durable complete responses in some leukemias and lymphomas, even in patients who have suffered multiple relapses.



## Limitations of Current Cellular Immunotherapy Approaches.

Despite rapid advances in various approaches to cellular immunotherapy and the biopharmaceutical industry's considerable investment in research and development, certain challenges have prevented these therapies from realizing their maximum potential. Some of these obstacles and issues are highlighted below:

### Our Proprietary CID Technology Platform

Our proprietary CID technology platform is designed to address the challenges of current cellular immunotherapies. Cellular activities and functions, such as growth, activation, proliferation and cell death, are controlled by cascades of specialized signaling proteins. Our CID platform consists of molecular switches, modified forms of these signaling proteins, which are triggered inside the patient by infusion of a small molecule, rimiducid, instead of by natural upstream signals. Our product candidates are based on either a "safety switch," or an "activation switch." After rimiducid is administered, the "safety switch" is designed to lead to programmed cell death, or apoptosis, and the "activation switch" is designed to lead to proliferation and/or activation of immune cells.

We incorporate the molecular switches in the appropriate immune cells and administer them to the patient. After the modified immune cells are inside the patient's body, specific functions of these cells may be controlled by administering rimiducid by intravenous, or IV, infusion. Rimiducid has been designed to bind to a specifically designed domain of CID switch proteins. Once introduced, rimiducid couples, or dimerizes, CID switch proteins together to create a cluster that triggers the signaling cascade. Aside from its impact on CID-modified immune cells bearing switch proteins, rimiducid has no other known effect on the body. To date, rimiducid has been used in more than 150 infusions in humans without any reported serious adverse events related to rimiducid.

Our proprietary CID-based product candidates depend on the following signaling molecules to trigger signaling cascades, resulting in different cell activities:

- Caspase-9: Signaling Molecule for Apoptosis. Caspase-9 is the initiating enzyme in the apoptosis pathway. When activated, caspase-9 starts a signaling cascade, including the activation of caspase-3, which ultimately leads to apoptosis, a non-inflammatory process of cell elimination.
- MyD88/CD40: Signaling Molecules for Activation and Proliferation. Myeloid differentiation primary response gene, or MyD88, is a protein that has functions in cellular responses to stimuli such as stress, cytokines and bacteria or viruses. CD40 is a co-stimulatory protein found on antigen-presenting cells, such as dendritic cells and B cells and is required for their activation. Although the effects of MyD88 and CD40 have been studied previously in dendritic cell therapies, our novel approach applies them to T cell based immunotherapies.

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## Our Proprietary Switch Technologies

With the CID platform as the foundation, we have created different molecular switch technologies customized for specific cellular immunotherapy approaches and therapeutic indications. The table below summarizes our key switch technologies.

### CaspaCIDE

CaspaCIDE is our CID safety switch technology designed to eliminate cells in the event of toxicity. The CaspaCIDE switch consists of the CID-binding domain coupled to the signaling domain of caspase-9, an enzyme that is part of the apoptotic pathway. Infusion of rimiducid is designed to trigger activation of this domain of caspase-9 (iCasp9), which in turn leads to selective apoptosis of the CaspaCIDE-containing cells. Because CaspaCIDE is designed to be permanently incorporated into our cellular therapies, the safety switch has the potential to be available for use long after the initial therapy is delivered. This technology is applied to our lead clinical product candidate, BPX-501, an adjunct T-cell therapy after allogeneic HSCT, and to our TCR product candidate, BPX-701.

We believe that CaspaCIDE is the optimal cell therapy safety switch technology. The only other widely reported approach used in the clinic is based on the Herpes simplex virus thymidine kinase, or HSV-tk, a non-human and as such immunogenic protein which is activated to kill the cell by the widely-used anti-viral drug, ganciclovir. Comparative studies have demonstrated CaspaCIDE's superiority to HSV-tk, based on lack of immunogenicity, effectiveness in rescuing animals from toxicities that have progressed, lack of dependence on the cell cycle for cell elimination, and most importantly, speed of elimination. In human trials, CaspaCIDE has demonstrated clinical efficacy in human patients beginning as soon as 30 minutes after administration of the activating drug, rimiducid. Lastly, rimiducid is bio-inert in the absence of cells containing a CID switch, and has no other clinical use; ganciclovir has side effects, and physicians are reluctant to lose the ability to use it to treat viral infections in patients treated with cells containing HSV-tk.

Other cell elimination approaches described in the literature include gene modification of cells to express truncated epidermal growth factor receptor, or EGFRt, or codon-optimized CD20. Administration of the monoclonal antibodies cetuximab or rituximab, respectively, is intended to trigger antibody-dependent cellular cytotoxicity, or ADCC, mediated cell elimination. While CaspaCIDE eliminates cells via the apoptotic pathway, the body's non-inflammatory mechanism for this important function, we believe an ADCC-mediated mechanism may add to complications in patients already in an inflammatory crisis, such as seen with serious cytokine

release syndrome after CAR T cell therapy. Moreover, cetuximab and rituximab, both anti-cancer therapies that have potentially serious side effects, are unlikely to be usable in a titratable manner. Lastly, these approaches have yet to demonstrate efficacy in clinical trials.

CaspaCIDE has been evaluated in both preclinical and clinical studies, with additional Phase 1/2 clinical trials ongoing and planned. In addition to using our CaspaCIDE technology for the substantial elimination of cellular therapy (like an “off” switch), we are studying partial elimination of a cellular therapy (like a “dimmer” switch) by delivering reduced doses of rimiducid. We observed the dose response to rimiducid by measuring the viability of BPX-501 cells in culture following the addition of increasing amounts of rimiducid to the culture medium as well as by measuring the survival of BPX-501 cells in vivo in immune-deficient mice following injection of increasing doses of rimiducid. In these preclinical studies, rimiducid rapidly and consistently reduced or eliminated CaspaCIDE-containing cells in a dose-dependent manner.

In addition to our internal preclinical and clinical development activities, we are collaborating with renowned cancer research centers with expertise in cellular immunotherapy to apply our CaspaCIDE safety switch to the collaborators’ CAR-T product candidates. The National Cancer Institute, or NCI, has initiated a Phase 1/2 clinical trial for sarcoma and other solid tumors with a CAR construct targeting a solid tumor antigen combined with CaspaCIDE. Although we are not the sponsor of this clinical trial, we believe that it may extend clinical proof of principle for CaspaCIDE from the HSCT setting to the CAR T cell setting.

#### CIDeCAR

CIDeCAR consists of a CAR T cell that utilizes MC, our proprietary novel dual co-stimulatory domain, for improved T-cell activation and proliferation, and the CaspaCIDE safety switch. CAR interaction with cancer cell antigens complements MC signaling, which then leads to activation of T cells. In the event of serious toxicity, rimiducid activation of caspase-9 is designed to eliminate the CIDeCAR T cells.

In order to improve the effectiveness of CAR T cells in settings other than blood cancers located principally in the bone marrow, such as leukemia, some researchers have been working to develop “armored CARs” in which supplemental co-stimulatory signals or pro-inflammatory cytokines are added to the CAR T cells. Like an “armored CAR,” we include MC in our CIDeCAR technology in order to increase the potency of the therapy in these indications. While promising, these approaches may exacerbate safety issues found in standard CARs, such as cytokine release syndrome. We incorporate CaspaCIDE into CIDeCAR to address these safety concerns.

In proof-of-principle preclinical studies of CIDeCAR technology, CIDeCAR candidate BPX-401 and a solid tumor CIDeCAR targeting Her2, both of which incorporate MC, in place of the standard co-stimulatory molecules CD28, 4-1BB, or both together, were evaluated in vitro. These preclinical studies show that CIDeCAR technology results in enhanced activation, proliferation and tumor cell killing compared to standard comparator CARs. In addition, these studies demonstrate elimination of the CIDeCAR T cells after exposure to rimiducid.

Preclinical animal studies have shown that BPX-401 cells exhibit both anti-tumor activity and partial or complete elimination of T cells after administration of rimiducid in an NSG mouse Raji tumor model.

#### GoCAR-T

Our GoCAR-T technology incorporates a switch that activates CAR T cells when triggered by both rimiducid and the targeted antigen expressed on the surface of the cancer cells. Current generation CAR T cell constructs consist of a CD3 domain and one or more co-stimulatory molecules that are both activated when a cancer antigen binds to the portion of the chimeric antigen receptor on the outside of the engineered T cell. This reliance on antigen for activation of the CAR T cell results in an unpredictable and inherently uncontrollable therapeutic effect. For example, CAR T cells that target the CD19 receptor have been shown to proliferate in excess of 100,000-fold in some patients, to

comprise over 50% of circulating lymphocytes. Solid tumor CAR T cells, on the other hand, often fail to proliferate or persist at all for more than a few days or weeks and have been largely ineffective. In each situation, the physician has no effective way to intervene to achieve greater consistency, once the cells have been administered.

Our GoCAR-T technology is designed to change the current paradigm by separating the CIDE CAR dual co-stimulatory domain, MC, from the antigen recognition domain and moving it onto a separate molecular switch that can be controlled by rimiducid. GoCAR-T cells are designed to only be fully activated when exposed to both the cancer cells and rimiducid. This separation is designed to control the degree of activation of the CAR T cells through adjustments to the schedule of rimiducid administration, but still in a tumor-dependent manner.



In a proof-of-principle in vitro study of our GoCAR-T technology, GoCAR-T cells targeting the PSCA antigen can only be fully activated when the GoCAR-T cells are exposed to both their target PSCA-expressing human pancreatic cancer cells and rimiducid. In in vivo studies of GoCAR-T technology, target antigen PSCA-expressing Capan-1 human pancreatic tumors were established in immune-deficient, or NSG, mice were controlled by administration of GoCAR-T cells targeting PSCA and twice weekly administration of rimiducid.

We believe these studies together provide proof-of-principle that GoCAR-T technology may allow rimiducid to modulate the therapeutic effect from initiation of treatment, turning CAR T cell therapy from an uncontrollable, and largely unpredictable class into a more predictable therapy which can be adjusted, like a small molecule, to the patient's therapeutic window to the appropriate level.

## DeCIDE

DeCIDE technology is used to control the activation of dendritic cells. Dendritic cells are an important part of the immune system, processing antigens for presentation to T cells. Optimal stimulation of dendritic cells requires the activation of both the CD40 and toll-like receptor, or TLR, pathways, which results in maturation and activation of the dendritic cells as well as production of key cytokines, such as IL-12. These processes lead to a therapeutic response to the antigen by the patient's immune system. The potency of an immune response is governed by the maturation of dendritic cells in the patient's lymph nodes as well as the duration of interaction between activated dendritic cells with circulating T cells.

To take control of the activation of the dendritic cells and the resulting immune response to cancer, we have taken the signaling domains of CD40 and MyD88, and coupled them to our CID binding domain, to create our inducible MC switch, which we then insert into dendritic cells along with the PSMA antigen. Upon exposure to rimiducid, DeCIDE-containing dendritic cells are designed to become highly activated in a process that is no longer susceptible to being turned off by MMP. Our DeCIDE technology, thus, potentially enables us to activate dendritic cells with rimiducid after the patient has been vaccinated and the dendritic cells have migrated to the draining lymph nodes in a potent and long-lasting manner.

Fully activated dendritic cells exhibit a number of important traits, including increases to the levels of important cell surface markers, and production of important cytokines, such as IL-12. Cultured BPX-201 cells, which are dendritic cells transduced with our DeCIDE switch technology, produce increased levels of IL-12 in response to rimiducid. These data suggest that in addition to the temporal control of dendritic cell activation that DeCIDE technology affords, once exposed to rimiducid, DeCIDE-containing dendritic cells become highly activated, which may lead to more potent anti-cancer activity in patients.

## Our Product Candidates

### BPX-501: CaspaCIDE Product Candidate for Hematological Diseases

BPX-501 is an adjunct T-cell therapy administered after allogeneic HSCT that incorporates our CaspaCIDE technology. We are developing BPX-501 in the initial indications of hematological cancers and orphan inherited blood disorders. In the indication of hematological cancers, we are pursuing two regulatory pathways: (1) support of immune system recovery following allogeneic HSCT, and (2) the treatment of the relapse of underlying disease following allogeneic HSCT. In orphan inherited blood disorders, we are pursuing a parallel regulatory pathway for immune system recovery following allogeneic HSCT.

We are currently conducting three Phase 1/2 clinical trials of BPX-501 at leading transplant centers in the United States and Europe: BP-001, a clinical trial in adults in which BPX-501 is administered after initial allogeneic HSCT for hematological cancers, BP-003, a clinical trial in children with orphan inherited blood disorders in which BPX-501 is administered after initial allogeneic HSCT, and BP-004 an additional Phase 1/2 clinical trial in children with

hematological cancers or orphan inherited blood disorders. In addition, we are planning to initiate additional Phase 1/2 clinical trials in the United States and Europe in 2015, as part of our strategy to pursue a global regulatory approval and expand the potential addressable patient population for BPX-501.

#### BPX-201: DeCIDE Cancer Vaccine Product Candidate

We are developing BPX-201 as a dendritic cell cancer vaccine designed to treat mCRPC. BPX-201 is an autologous therapy, in which the patient's own white blood cells are extracted and modified *ex vivo*. The cells are matured and then genetically engineered to express the DeCIDE switch domains and the PSMA antigen. Then, the modified cells are washed, apportioned into individual doses, and frozen for later administration to the patient.

By incorporating the DeCIDE switch that activates therapy only in the presence of rimiducid, physicians may be able to strategically time the immune system's attack on cancer cells. The rationale behind this approach is to allow BPX-201 cells to bypass critical immune checkpoints that can potentially reduce therapeutic effect and migrate to nearby lymph nodes to initiate a potent and durable antigen-specific T-cell response.

We submitted an IND for BPX-201 in September 2012 and it is currently being evaluated in an 18-patient Phase 1 clinical trial for mCRPC. The clinical trial design consists of three cohorts of six patients each, who will receive escalating doses of BPX-201. The patients will be followed for two years after enrollment.

We are evaluating opportunities for BPX-201 in combination with other cancer immunotherapies, such as checkpoint inhibitors. Checkpoint inhibitors act by removing inhibitory signals on antigen- or tumor- specific T cells already present in the patient's body. BPX-201 shows the potential to stimulate proliferation of PSMA-specific T cells thereby providing a rationale to successfully combine BPX-201 with checkpoint inhibitors.

#### BPX-401: CIDE CAR Product Candidate for Hematological Cancers

We are developing BPX-401 for the treatment of hematological cancers expressing the CD19 antigen, such as ALL, CLL and certain types of non-Hodgkin's lymphoma. We have generated preclinical proof-of-principle data in vitro showing that BPX-401 has significant CAR T cell activation and proliferation potential, and may be more effective in killing cancer cells compared to other CAR-T constructs. We intend to file an IND and initiate a Phase 1/2 clinical trial in the first half of 2016.

The current standard of care in these indications, chemotherapy combined with monoclonal antibody therapies, works to varying degrees with high disease relapse rates. CD19-targeted CAR-T therapies have elicited high objective response rates in some of these B cell cancers, but they have demonstrated major safety risks.

#### BPX-601: GoCAR-T Product Candidate for Solid Tumors

We are currently conducting preclinical studies of BPX-601 for the treatment of solid tumors overexpressing the PSCA antigen. PSCA is highly expressed in some pancreatic cancers, as well as in a portion other solid tumors, including bladder, esophageal and gastric cancers. Although many product candidates are in development for these cancers, there are currently no approved products targeting PSCA. We intend to initiate a Phase 1/2 clinical trial in the second half of 2016. In order to commercialize this product candidate, we may need to obtain an additional intellectual property license.

#### BPX-701: CaspaCIDE TCR Product Candidate for Solid Tumors

We are developing BPX-701, a TCR-based therapy that incorporates our CaspaCIDE technology, in collaboration with Leiden University Medical Center, for the treatment of PRAME-expressing melanoma, sarcomas and neuroblastomas. We intend to file an IND and initiate a Phase 1/2 clinical trial by the end of 2015. Clinical sites for this trial have been identified.

BPX-701 is designed to target preferentially-expressed antigen in melanoma, or PRAME, a gene that is predominantly expressed in human melanomas but not in normal tissues. As initially reported in Clinical Cancer Research 2011, PRAME-specific clones showed high reactivity against a panel of PRAME positive tumor cell lines, metastatic melanoma, sarcomas and neuroblastoma tissues, and no reactivity against normal cell types, with the exception of low reactivity against kidney epithelial cells and intermediate reactivity against mature dendritic cells, or DCs. In other TCR programs, despite careful evaluation of normal tissues to identify potential off target effects, unexpected cross-reactivities have been encountered in clinical trials, leading to serious adverse events including patient deaths. BPX-701 containing the CaspaCIDE safety switch, has demonstrated complete elimination in response to rimiducid. Therefore, we believe a PRAME-TCR with CaspaCIDE can provide safety in the clinical development of this TCR.

#### Other Development Programs

We believe that our CIDE CAR, GoCAR-T and CaspaCIDE TCR technologies have broad applicability against a range of cancer targets which form the basis for additional development programs, some of which are described below:

#### CIDeCAR for Solid Tumors

Beyond hematological cancers, we are studying the full potential of CIDeCAR to enable treatment of more challenging solid tumor cancers in which concerns regarding toxicity are paramount in the field of cell therapy. To this end, we are conducting preclinical studies of various CIDeCAR product candidates targeting solid tumor antigens.

#### CaspaCIDE TCR for Hematological Cancers

We are working with our collaborator, Leiden University Medical Center, to evaluate an additional TCR with high affinity for certain peptides for the treatment of hematological cancers, including ALL, CLL, MCL and MM. The TCR construct incorporates the CaspaCIDE safety switch.

## Manufacturing, Processing and Delivering to Patients

Our product candidates require a combination of three critical components: (1) viral vectors with DNA content encoded for our proprietary switch proteins and co-stimulatory and other accessory molecules, (2) patient-specific donor T cells or dendritic cells that are genetically modified by our viral vectors, and (3) the synthetic small molecule rimiducid which activates the switch proteins. Each of these components requires a separate supply chain and shares the same regulatory requirements applicable for biological or chemical materials suitable for human use. Details on each of these components are described below:

- **Viral Vectors.** We use a retrovirus to transduce our T cell based product candidates. We believe that the retrovirus is optimal for T cell transduction given that it is an integrating vector that induces long-term gene expression, exhibits high transduction efficiency, has large capacity for DNA content, and has been safely used in clinical trials. As an alternative approach, we are investigating in parallel the use of lentivirus for several of our product candidates. In certain embodiments, lentiviral vectors may provide advantages over retroviral vectors. To transduce dendritic cells, we use a specific type of adenovirus, which has been shown to be efficient at transducing this cell type and is cost-effective to manufacture and scale. The vector production is performed at multiple third-party supplier facilities under GMP procedures and requirements. These suppliers have significant experience and expertise in vector manufacturing and have dedicated capacity to satisfy demand for large clinical trials and product commercialization.
- **Genetically Modified T Cells and Dendritic Cells.** We have agreements with reputable contract manufacturing organizations, or CMOs, with facilities in both the United States and Europe for processing and manufacturing our genetically modified T cells and dendritic cells. We have designed and refined a proprietary process for cell engineering that has been improved from lab-based open procedures used in academic and research settings to a functionally closed system that is more appropriate for large-scale clinical trials and commercialization. Our system is compliant with current guidelines and regulations for cell-based manufacturing in the United States and Europe and has been successfully transferred and implemented by our CMOs.
- **Rimiducid.** Rimiducid is a synthetic small molecule which has been rationally designed to trigger the proprietary switch proteins in our CID platform. We have separate third-party manufacturers for the active pharmaceutical ingredient, or API and the finished drug product. Manufacturers of both the API and finished drug product are licensed to manufacture a variety of marketed drugs worldwide and have been selected based on their ability to provide supplies for our clinical trials and future commercialization.

Given that our product candidates are for patients whose conditions can rapidly deteriorate, we are focused on continuously refining our overall cell therapy process (manufacturing, processing and delivery to patient) to be more efficient.

Our current process cycle from our product candidates, from collection of white blood cells to infusion of the final product, can be completed in as little as two weeks and are customized to be complementary to the treatment procedure of interest in order to prevent any delays or complications.

## Intellectual Property

We seek to protect proprietary technology, inventions, and improvements that are commercially important to our business by seeking, maintaining, and defending patent rights, whether developed internally or licensed from third parties. We also seek to rely on regulatory protection afforded through orphan drug designations, data exclusivity, market exclusivity and patent term extensions where available as well as contractual agreements with our academic and commercial partners.

To achieve this objective, a strategic focus for us has been to identify and license key patents and patent applications that serve to enhance our intellectual property and technology position. Our intellectual property estate includes: (1) claims directed to core CID technologies and components used in our products; (2) claims directed to methods of treatment for therapeutic indications; (3) claims directed to specific products; and (4) claims directed to innovative methods for generating new constructs for genetically engineering T cells and dendritic cells. We believe our patent

estate, together with our efforts to develop and patent next generation technologies, provides us with a substantial intellectual property position.

However, the area of patent and other intellectual property rights in biotechnology is an evolving one with many risks and uncertainties. We are aware there are third party patents having claims that may be considered relevant to the BPX-201 technology for which we are seeking, regulatory approval, however, we believe these patents have a patent term that may expire prior to the time we expect to obtain regulatory approval for this technology. We believe that if claims in one or more of the patents referenced in the previous sentence are asserted against us, we may be able to assert a defense for a safe harbor to patent infringement under 35 U.S.C. 271(e)(1) if certain requirements are met. Please refer to the section entitled “Item 1A. Risk Factors—Risks Related to Our Intellectual Property” herein for associated risks.

We are aware of a third party patent having claims directed to chimeric DNA comprising DNA segments encoding (1) a single chain antibody domain and (2) transmembrane and cytoplasmic domains of an endogenous protein. We believe that our BPX-401 and BPX-601 technologies are not covered by claims of this patent. Please refer to the section entitled “Item 1A. Risk Factors—Risks Related to Our Intellectual Property” herein for associated risks.

We are aware of third party patents having claims that may be considered as being directed to single-chain antibody fragments that bind to PSCA and these patents may be considered relevant to BPX-601 technologies we are developing. We currently are evaluating whether or not we need to obtain rights to these patents under a license, and if it is determined that we need to obtain such rights, whether these rights can be obtained. Please refer to the section entitled “Item 1A. Risk Factors—Risks Related to Our Intellectual Property” herein for associated risks.

To our knowledge, our patent estate, on a worldwide basis, includes 75 issued patents 18 of which are in the United States) and 47 pending patent applications (20 of which are in the United States) which we own or for which we have an exclusive (either in its entirety or within our field of use) commercial license as of March 13, 2015. Of these:

§ We have internally developed technology disclosed in one pending provisional patent application and three utility patent applications in the United States, and three pending international (PCT) patent applications which relate to our CIDECAR technology. If the provisional patent application is converted to a utility patent application, and a U.S. patent issues therefrom, the estimated expiration date of the last to expire patent is in 2035 or later. If patents are issued in foreign jurisdictions, the anticipated expiration date of the last to expire patent will also be in 2035.

§ We have internally developed technology disclosed in two pending utility patent applications in the United States and two pending international (PCT) patent applications which relates to our GoCAR-T technology. If U.S. patents issue from the US applications, the estimated expiration date of the last to expire patent is in 2034 or later. If patents are issued in foreign jurisdictions, the anticipated expiration dates will be in 2034 or later.

§ We have internally developed technology disclosed in two U.S. provisional patent applications, which relates to a “non-inducible” CAR and “non-inducible” co-stimulatory polypeptide, which may also be used in combination with our CIDECAR technology. If either of these provisional patent applications is converted to a utility patent application, and a U.S. patent issues from it, the estimated expiration date of the patent is 2035 or later. If patents are filed and issued in foreign jurisdictions, the anticipated expiration dates will be in 2035 or later.

§ Pursuant to our licenses from Baylor, we have exclusive commercial rights to three issued U.S. patents expiring in 2024 or later, seven pending U.S. utility patent applications, one issued patent in Australia expiring in 2027, one issued patent in Australia expiring in 2031 and 21 pending patent applications in foreign jurisdictions that relate to our GoCAR-T, BPX-201 and certain of our other technologies. If U.S. patents issue from the currently pending U.S. patent applications, the estimated expiration date of the last to expire patent is 2031 or later. Patent applications have been filed in foreign jurisdictions, including Australia, Canada, Europe, Hong Kong and Japan. If patents from the currently pending patent applications are issued in foreign jurisdictions, the estimated expiration dates range from 2024 to 2029.

§ Pursuant to our license agreement with ARIAD, as amended, we have exclusive commercial rights within our field of use to 69 patents (14 in the United States and 55 in foreign jurisdictions, including Australia, Canada, China, Europe, Japan and Korea), which relate to dimerizer technology. The estimated expiration date of the last to expire U.S. patent is February 2016. The estimated expiration dates of the last to expire foreign patents are between 2015<sup>1</sup> and 2020. Also pursuant to this license agreement, we have exclusive commercial rights within our field of use to two pending applications (one in the United States and one in Australia) which relate to dimerizer technology. If a U.S. patent issues from the currently pending U.S. patent application, the estimated expiration date of the last to expire patent is 2032 or later. If a patent issues in Australia from the currently pending application, the estimated expiration date is 2031.

These provisional, pending, or issued patents include composition of matter and/or method of use claims.

As noted above, patent coverage on rimiducid, the dimerization molecule AP1903, will expire in the U.S. in 2016. However, we believe that additional barriers to entry exist for a competitor attempting to use rimiducid after patent expiration. This is significant because, if true, then potential competitors will not be able to use the abbreviated new drug application pathway for approval of rimiducid. With respect to our investigational products, the FDA has assigned combination product status to BPX-501, and we plan to submit a biological license application, or BLA, for the combination product. We believe that this will be the case for each future product candidate of ours that incorporates rimiducid. If our investigational products incorporating rimiducid receive FDA approval through BLAs, then the FDA would not approve any biosimilar of these combination products until at least 12 years from the date that we receive FDA approval. Additionally, although 'biosimilar' provisions exist for products approved through BLAs, it is not clear if the FDA will permit the biosimilar route to be used for complex biological products such as our investigational products.

Rimiducid is a relatively complex drug substance to manufacture. We have substantial experience in manufacturing of rimiducid and in preparing it for patient infusion. Our manufacturing know-how is a valuable asset and we incorporate contractual confidentiality terms in all agreements with our third party manufacturers. We believe that a competitor will face substantial obstacles with respect to time and cost in order to derive a clinically acceptable manufacturing process.

Our strategy is also to develop and obtain additional intellectual property covering manufacturing processes and methods for genetically engineering T cells expressing new constructs. To support this effort, we have established expertise and development capabilities focused in the areas of preclinical research and development, manufacturing and manufacturing process scale-up, quality control, quality assurance, product delivery and storage, regulatory affairs and clinical trial design and implementation. As appropriate, we expect to file additional patent applications to expand this layer of our intellectual property estate.

The term of individual patents depends upon the legal term of the patents in the countries in which they are obtained. In most countries in which we file, the patent term is 20 years from the date of filing of the first non-provisional application to which priority is claimed. In the United States, a patent's term may be lengthened by patent term adjustment, which compensates a patentee for administrative delays by the U.S. Patent and Trademark Office in granting a patent, or may be shortened if a patent is terminally disclaimed over an earlier-filed patent. The term of a patent that covers an FDA-approved drug or biologic may also be eligible for a patent term restoration of up to five years under the Hatch-Waxman Act, which is designed to compensate for the patent term lost during the FDA regulatory review process. The length of the patent term restoration is calculated based on the length of time the drug or biologic is under regulatory review. A patent term restoration under the Hatch-Waxman Act cannot extend the remaining term of a patent beyond a total of 14 years from the date of product approval and only one patent applicable to an approved drug or biologic may be restored. Moreover, a patent can only be restored once, and thus, if a single patent is applicable to multiple products, it can only be extended based on one product. Similar provisions are available in Europe and certain other foreign jurisdictions to extend the term of a patent that covers an approved drug or biologic. When possible, depending upon the length of clinical trials and other factors involved in the filing of a BLA we expect to apply for patent term extensions for patents covering our product candidates and their methods of use.

We may rely, in some circumstances, on trade secrets to protect our technology. We seek to protect our proprietary technology and processes, in part, by entering into confidentiality agreements with our employees, consultants, scientific advisors and contractors. We also seek to preserve the integrity and confidentiality of our data and trade secrets by maintaining physical security of our premises and physical and electronic security of our information technology systems. While we have confidence in these individuals, organizations and systems, agreements or security measures may be breached, and we may not have adequate remedies for any breach. In addition, our trade secrets may otherwise become known or be independently discovered by competitors. To the extent that our



consultants, contractors or collaborators use intellectual property owned by others in their work for us, disputes may arise as to the rights in related or resulting know-how and inventions.

#### Our License Agreements

##### License Agreement with ARIAD Pharmaceuticals, Inc.

##### 2011 License Agreement

On March 7, 2011, we entered into an amended and restated exclusive license agreement, or restated ARIAD license, with ARIAD which restated a license agreement entered into in 2006. Under the restated ARIAD license, ARIAD granted to us an exclusive (even as to the ARIAD) license, with the right to grant sublicenses, under ARIAD's patent rights relating to dimerizers, genetic constructs coding for dimerizer binding domains, vectors containing said constructs, cells containing said constructs and methods of inducing biological processes in cells containing said constructs. These licensed patent rights were limited in the 2011 restated license to defined products in the fields of cell transplantation and certain types of cancer.

In connection with the initial license, in 2006, we issued 121,242 shares of our common stock to ARIAD which were subject to antidilution protection that ultimately resulted in additional issuances to ARIAD by us of 556,221 shares of our common stock, such that ARIAD received a total of 677,463 shares of our common stock under the license agreement. In addition, we paid ARIAD a license fee of \$250,000 in connection with the restatement in 2011. The restated ARIAD license also provided for certain royalty and milestone payments, which were subsequently terminated pursuant to an omnibus amendment agreement with ARIAD (see below).

Under the restated ARIAD license, we are required to diligently proceed with the development, manufacture and sale of licensed products. The restated ARIAD license is subject at all times to restrictions and obligations under a license agreement by and between ARIAD Gene Therapeutics, Inc. (one of ARIAD's affiliates which merged into ARIAD) and the academic institution from which ARIAD obtained its license to the underlying technology. While we are not required to pay royalties or fees to such academic institution, no sub licensee of ours may enter into a sublicense with respect to any intellectual property owned by the academic institution without its consent, which terms must be consistent with those included in the agreement between ARIAD and such academic institution.

The restated ARIAD license will expire upon expiration of the last license term of a licensed product covered by the agreement, which is the later of (1) 12 years from the date of the first commercial sale of the licensed product, or (2) the expiration of the last to expire valid patent claim on the licensed product. Either party to the license may terminate or modify the restated ARIAD license upon a material breach by the other party that remains uncured following the date that is 30 days after written notice of a payment breach and 90 days for any other breach, and effective immediately upon bankruptcy of the other party. We may terminate the restated ARIAD license in our sole discretion at any time if we determine not to develop or commercialize any licensed product. In addition, upon termination of the restated ARIAD license prior to expiration, we must transfer any ownership and any beneficial ownership in any orphan drug designation or any similar designation in any jurisdiction of orphan drug status of the ARIAD dimerizer to ARIAD.

#### 2014 Amendment

In October 2014, we entered into an omnibus amendment agreement with ARIAD, which in part amended the restated ARIAD license to expand the license to cover a broader scope of dimerizers and licensed products for use and exploitation in any human therapeutic field of use other than in vivo administration of genetic material directly into a human being using viral vectors for the purpose of producing proteins or other macromolecules that are expressed or secreted for therapeutic or prophylactic purposes.

In connection with the amendment, we made an initial payment of \$15,000,000 and we issued a promissory note to ARIAD for a principal amount of \$35,000,000 in return for the broader scope of the license and the termination of all obligations to make milestone and royalty payments to ARIAD in the future. On December 23, 2014, the closing of our initial public offering triggered an acceleration of the payment of \$15,000,000 due to ARIAD under the amendment and the promissory note. As a result of such acceleration, on December 29, 2014, we paid to ARIAD an aggregate amount of \$35,000,000, which included an additional payment of \$20,000,000 to extinguish the promissory note. In exchange, ARIAD returned to us all of the 677,463 shares of our common stock then held by ARIAD and all of the agreements related to ARIAD's rights as a stockholder of us were terminated.

#### License Agreements with Baylor College of Medicine

##### 2008 Baylor License Agreement

Pursuant to an Exclusive License Agreement with Baylor College of Medicine, or Baylor, dated March 20, 2008, or the 2008 Baylor license agreement, we obtained an exclusive, worldwide and fully paid up license to certain intellectual property, including intellectual property related to methods for activating antigen presenting cells and to genetic constructs coding for membrane bound inducible cytoplasmic CD40.

As consideration for the 2008 Baylor license agreement, we issued to Baylor 23,529 shares of our common stock and assumed responsibility for all legal fees and expenses, filing or maintenance fees, assessments and all other costs and expenses related to prosecuting, obtaining and maintaining patent protection on the patents subject to the 2008 Baylor license agreement.

The 2008 Baylor license agreement is subject to certain restrictions and is nonexclusive with respect to (1) the making or use of the licensed intellectual property for use in non-commercial research, patient care, teaching, and other educational purposes; (2) any non-exclusive license covering the licensed intellectual property that Baylor grants to other academic or research institutions for noncommercial research purposes; (3) any non-exclusive licenses that Baylor is required to grant to the U.S. or foreign state pursuant to an existing or future treaty with the U.S.; and (4) a non-exclusive license granted to ARIAD under the terms of a materials transfer agreement between Baylor and ARIAD.

Baylor may terminate or modify the 2008 Baylor license agreement in the event of a material breach that remains uncured following the date that is 90 days after written notice of such breach or upon certain insolvency events that remain uncured following the date that is 30 days following written notice of such insolvency event. We may terminate the 2008 Baylor license agreement, or any portion thereof, at our sole discretion at any time upon 30 days' written notice to Baylor. Upon termination of the 2008 Baylor license agreement, all rights to the intellectual property immediately revert to Baylor.

#### 2010 Baylor License Agreement

Pursuant to an Exclusive License Agreement with Baylor, dated June 27, 2010, or the 2010 Baylor license agreement, we obtained an exclusive, worldwide license to certain intellectual property, including intellectual property related to methods for treating prostate cancer, methods of administering T cells to a patient, and methods of activating antigen presenting cells with constructs comprising MyD88 and CD40.

Pursuant to the terms of the 2010 Baylor license agreement, we paid Baylor a license execution fee of \$30,000. In addition, we are required to pay a low annual maintenance fee on each anniversary of the agreement date.

The terms of the 2010 Baylor license agreement also require us to make royalty payments of less than one percent, subject to certain annual minimums, on net sales of products covered by the license. In addition, to the extent we enter into a sublicensing agreement relating to a licensed product, we are required to pay Baylor a percentage in the mid-single digits on all non-royalty income received from sublicensing revenue. We are required to make milestone payments, of up to \$735,000 in aggregate, upon successful completion of clinical and regulatory milestones regarding the first two products covered by this license.

The 2010 Baylor license agreement will expire upon expiration of the last patent contained in the licensed patent rights, on a country-by-country basis, upon which we will have a perpetual, paid-in-full license in such country. Baylor may terminate or modify the 2010 Baylor license agreement in the event of a material breach by us that remains uncured following the date that is 90 days after written notice of such breach or upon certain insolvency events that remain uncured following the date that is 30 days following written notice of such insolvency event. We may terminate the 2010 Baylor license agreement, or any portion thereof, at our sole discretion at any time upon 60 days' written notice to Baylor. Upon termination of the 2010 Baylor license agreement for any reason prior to expiration, we must assign to Baylor each authorized sublicense agreement that is currently in effect on the date of termination.

#### 2014 Baylor License Agreement

Pursuant to an Exclusive License Agreement with Baylor, effective November 1, 2014, or the 2014 Baylor license agreement, we obtained an exclusive, worldwide license to certain intellectual property, including intellectual property related to methods for inducing selective apoptosis.

Pursuant to the terms of the 2014 Baylor license agreement, we paid Baylor a license execution fee of \$25,000. In addition, we are required to pay Baylor a low annual maintenance fee on each anniversary of the agreement date. The terms of the 2014 Baylor license agreement also require us to make royalty payments in the low single digits, subject to certain annual minimums, on net sales of products covered by the license. To the extent we enter into a sublicensing agreement relating to a licensed product, we are also required to pay Baylor a percentage in the low double-digits on all non-royalty income received from sublicensing revenue. We are required to make milestone payments, of up to \$275,000 in aggregate, upon successful completion of clinical and regulatory milestones regarding the first product covered by this license. The 2014 Baylor license agreement will expire upon expiration of the last patent contained in the licensed patent rights, on a country-by-country basis, upon which we will have a perpetual, paid-in-full license in each such country.

Baylor may terminate or modify the 2014 Baylor license agreement in the event of a material breach by us that remains uncured following the date that is 90 days after written notice of such breach or upon certain insolvency events that remain uncured following the date that is 30 days following written notice of such insolvency event. We may terminate the 2014 Baylor license agreement, or any portion thereof, at our sole discretion at any time upon 60 days' written notice to Baylor.

#### Grant Agreement

##### Grant Agreement with Cancer Prevention and Research Institute of Texas

On July 27, 2011, we entered into a Cancer Research Grant Contract, or the Grant Contract, with the Cancer Prevention and Research Institute of Texas, or CPRIT, under which CPRIT awarded a grant not to exceed approximately \$5.7 million to be used by us for the execution of defined clinical development of BPX-501. In addition, CPRIT may award supplemental funding not to exceed ten percent of the total grant amount based upon our progress. To date, we have received approximately \$4.9 million under the grant. The Grant Contract terminated on June 30, 2014, but obligations exist as to licensing, royalty payments, and indemnification provisions.

Pursuant to the Grant Contract, we granted CPRIT with a non-exclusive, irrevocable, royalty-free, perpetual, worldwide license to the intellectual property facilitated by the Grant Contract for and on behalf of CPRIT and other governmental entities and agencies of the State of Texas for education, research and other non-commercial purposes only.

The terms of the Grant Contract require that we pay tiered royalties in the low- to mid-single digit percentages on revenues from sales and licenses of intellectual property facilitated by the Grant Contract. If a third party acquires substantially all of our assets, we have the option to buy out from the royalty obligations by paying a buyout amount that is equal to a percentage of the net grant award proceeds received by us under the Grant Contract, less the aggregate amount of all royalties paid at the time of the buyout. The applicable percentage depends on the timing of the buyout and ranges from 125% to 200%.

We are required to use diligent and commercially reasonable efforts to commercialize or otherwise bring to practical application the results of the funded clinical trial. If CPRIT notifies us of our failure to (1) make the required effort to commercialize any product covered by this agreement or (2) perform our obligations with respect to protection of intellectual property, the rights to any intellectual property and proprietary and confidential information may, at CPRIT's option, revert to CPRIT and CPRIT, at its own cost, can take over the prosecution and maintenance of any impacted patents and commercialize such product candidate. CPRIT's option is subject to our ability to cure any failures identified by CPRIT within 30 days.

## Competition

The biopharmaceutical industry is characterized by intense and dynamic competition to develop new technologies and proprietary therapies. Any product candidates that we successfully develop and commercialize will have to compete with existing therapies and new therapies that may become available in the future. While we believe that our proprietary CID platform, differentiated product candidates and scientific expertise in the field of cellular immunotherapy provide us with competitive advantages, we face potential competition from various sources, including larger and better-funded pharmaceutical, specialty pharmaceutical and biotechnology companies, as well as from academic institutions, governmental agencies and public and private research institutions.

Our lead product candidate, BPX-501, is an adjunct therapy for HSCT with alternative donors that potentially improves stem cell engraftment, accelerates host immune system recovery and treats GvHD. The current standard-of-care that addresses some of the safety challenges associated with HSCT, primarily GvHD, is high-dose steroids. We are aware of other companies that are developing product candidates to improve the outcome of HSCT, including Kiadis Pharma Netherlands B.V. and Molecular Medicine S.p.A.

T-cell based treatments for cancer, such as CAR-T and TCR therapies, have recently been an area of significant research and development by academic institutions and biopharmaceutical companies. BPX-401, BPX-601 and BPX-701 based on our CIDE CAR and Go-CART technologies will compete with product candidates from a number of companies that are currently focused on this therapeutic modality, including Adaptimmune Limited, bluebird bio, Inc., Celgene Corporation, Cellectis SA, GlaxoSmithKline plc, Intrexon Corporation, Juno Therapeutics, Inc., Kite Pharma, Inc., Novartis AG, Pfizer Inc. and Ziopharm Oncology.

BPX-201 based on our DeCIDE technology is a dendritic cell-based cancer vaccine for the treatment of metastatic prostate cancer and other solid tumors. PROVENGE®, marketed by Dendreon Corporation, is the first approved cancer vaccine for the treatment of mCRPC. We are aware of other companies focused on developing cancer vaccines, including Advaxis, Inc., Argos Therapeutics, Inc., Biovest International, Inc., ImmunoCellular Therapeutics, Ltd., Immune Design, Inc., Inovio Pharmaceuticals, Inc., Intrexon Corporation and Northwest Biotherapeutics, Inc.

Many of our competitors, either alone or with their strategic partners, have substantially greater financial, technical and human resources than we do and significantly greater experience in the discovery and development of product

candidates, obtaining FDA and other regulatory approvals of treatments and commercializing those treatments. Accordingly, our competitors may be more successful than us in obtaining approval for treatments and achieving widespread market acceptance. Our competitors' treatments may be more effective, or more effectively marketed and sold, than any treatment we may commercialize and may render our treatments obsolete or non-competitive before we can recover the expenses of developing and commercializing any of our treatments.

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

We anticipate that we will face intense and increasing competition as new drugs enter the market and advanced technologies become available. We expect any treatments that we develop and commercialize to compete on the basis of, among other things, efficacy, safety, convenience of administration and delivery, price, the level of generic competition and the availability of reimbursement from

government and other third-party payers. For example, if a third party is able to obtain a stand-alone new drug application for rimiducid, then potential generic manufacturers may be able to file abbreviated new drug applications for such product.

Our commercial opportunity could be reduced or eliminated if our competitors develop and commercialize products that are safer, more effective, have fewer or less severe side effects, are more convenient or are less expensive than any products that we may develop. Our competitors also may obtain FDA or other regulatory approval for their products more rapidly than we may obtain approval for ours, which could result in our competitors establishing a strong market position before we are able to enter the market. In addition, we expect that our therapeutic products, if approved, will be priced at a significant premium over competitive generic products and our ability to compete may be affected in many cases by insurers or other third-party payers seeking to encourage the use of generic products.

#### Government Regulation and Product Approval

As a biopharmaceutical company that operates in the United States, we are subject to extensive regulation. Our cell products will be regulated as biologics. With this classification, commercial production of our products will need to occur in registered and licensed facilities in compliance with cGMP for biologics.

The FDA regulates human cells, tissues, and cellular and tissue-based products, or HCT/Ps, under a two-tiered framework, based on risk categorization. Higher risk HCT/Ps are regulated as biologics. Manufacturers of biologics are subject to extensive government regulation. For example, such products must complete extensive clinical trials, which must be conducted pursuant to an effective investigational new drug application, or IND. The FDA must review and approve a BLA before a new biologic may be marketed.

The FDA considers our investigational products to be “combination products” because our products involve a biologic (the engineered cells) that is intended to be used with a small molecule chemical drug (AP1903, licensed from ARIAD). In general, biologics such as our engineered cells are regulated through FDA’s Center for Biologics Evaluation and Research, or CBER, while synthetic drugs are regulated through FDA’s Center for Drug Evaluation and Research, or CDER. When FDA encounters a combination product such as our products, the agency determines which of the two centers will have primary responsibility for regulating the product by determining the primary mode of action for the product. In this case, we believe that the cellular component of the combination contributes the primary mode of action and, as a result, that FDA will regulate our investigational products as biologics, through CBER.

Government authorities in the United States (at the federal, state and local level) and in other countries extensively regulate, among other things, the research, development, testing, manufacturing, quality control, approval, labeling, packaging, storage, record-keeping, promotion, advertising, distribution, post-approval monitoring and reporting, marketing and export and import of biopharmaceutical products such as those we are developing. Our product candidates must be approved by the FDA before they may be legally marketed in the United States and by the appropriate foreign regulatory agency before they may be legally marketed in foreign countries. Generally, our activities in other countries will be subject to regulation that is similar in nature and scope as that imposed in the United States, although there can be important differences. Additionally, some significant aspects of regulation in Europe are addressed in a centralized way, but country-specific regulation remains essential in many respects. The process for obtaining regulatory marketing approvals and the subsequent compliance with appropriate federal, state, local and foreign statutes and regulations require the expenditure of substantial time and financial resources.

#### U.S. Product Development Process

In the United States, the FDA regulates new drugs and biological products under the Federal Food, Drug and Cosmetic Act, or FDCA; the Public Health Service Act, or PHSA; and implementing regulations. Products are also subject to other federal, state and local statutes and regulations. The process of obtaining regulatory approvals and the



subsequent compliance with appropriate federal, state, 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, criminal, or civil sanctions. FDA sanctions could include, among other actions, refusal to approve pending applications, withdrawal of an approval, a clinical hold, warning letters, product recalls or withdrawals from the market, product seizures, total or partial suspension of production or distribution injunctions, fines, refusals of government contracts, restitution, disgorgement or civil or criminal penalties. Any administrative, criminal, or civil enforcement action could have a material adverse effect on us. The FDA has limited experience with commercial development of T cell therapies for cancer. The process required by the FDA before a biological product may be marketed in the United States generally involves the following:

- completion of nonclinical laboratory tests and animal studies according to good laboratory practices, or GLPs, and applicable requirements for the humane use of laboratory animals or other applicable regulations;
- submission to the FDA of an IND, which must become effective before human clinical trials may begin;

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- performance of adequate and well-controlled human clinical trials according to the FDA's regulations commonly referred to as good clinical practices, or GCPs, and any additional requirements for the protection of human research patients and their health information, to establish the safety and efficacy of the proposed biological product for its intended use;
- submission to the FDA of a BLA for marketing approval that includes substantial evidence of safety, purity, and potency from results of nonclinical testing and clinical trials;
- satisfactory completion of an FDA inspection of the manufacturing facility or facilities where the biological product is produced to assess compliance with cGMP, to assure that the facilities, methods and controls are adequate to preserve the biological product's identity, strength, quality and purity and, if applicable, the FDA's current good tissue practices, or GTPs, for the use of HCT/Ps;
- potential FDA audit of the nonclinical study and clinical trial sites that generated the data in support of the BLA; and
- FDA review and approval, or licensure, of the BLA.

Before testing any biological product candidate, including our product candidates, in humans, the product candidate enters the preclinical testing stage. Preclinical tests, also referred to as nonclinical studies, include laboratory evaluations of product chemistry, toxicity and formulation, as well as animal studies to assess the potential safety and activity of the product candidate. The conduct of the preclinical tests must comply with federal regulations and requirements including GLPs. The clinical trial sponsor must submit the results of the preclinical tests, together with manufacturing information, analytical data, any available clinical data or literature and a proposed clinical protocol, to the FDA as part of the IND. 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 raises concerns or questions regarding the proposed clinical trials and places the trial on a clinical hold within that 30-day time period. In such a case, the IND sponsor must resolve FDA's outstanding concerns before the clinical trial can begin. The FDA may also impose clinical holds on a biological product candidate at any time before or during clinical trials due to safety concerns or non-compliance. If the FDA imposes a clinical hold, trials may not recommence without FDA authorization and then only under terms authorized by the FDA. Accordingly, we cannot be sure that submission of an IND will result in the FDA allowing clinical trials to begin, or that, once begun, issues will not arise that suspend or terminate such clinical trials.

Clinical trials involve the administration of the biological product candidate to healthy volunteers or patients under the supervision of qualified investigators, generally physicians not employed by or under the trial sponsor's control. Clinical trials are conducted under protocols detailing, among other things, the objectives of the clinical trial, dosing procedures, subject selection and exclusion criteria, and the parameters to be used to monitor subject safety, including stopping rules that assure a clinical trial will be stopped if certain adverse events should occur. Each protocol and any amendments to the protocol must be submitted to the FDA as part of the IND. Clinical trials must be conducted and monitored in accordance with the FDA's regulations comprising the GCP requirements, including the requirement that all research patients provide informed consent. Further, each clinical trial must be reviewed and approved by an institutional review board, or IRB, at or servicing each institution at which the clinical trial will be conducted. An IRB is independent from the trial sponsor and is charged with protecting the welfare and rights of clinical trial participants and considers such items as whether the risks to individuals participating in the clinical trials are minimized and are reasonable in relation to anticipated benefits. The IRB also approves the form and content of the informed consent that must be signed by each clinical trial subject or his or her legal representative and must monitor the clinical trial until completed. Clinical trials also must be reviewed by an institutional biosafety committee, or IBC, a local institutional committee that reviews and oversees basic and clinical research conducted at that institution. The IBC assesses the safety of the research and identifies any potential risk to public health or the environment.

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

- Phase 1. The biological product is initially introduced into healthy human subjects and tested for safety. 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 is often conducted in patients.

·Phase 2. The biological product is evaluated in a limited patient population to identify possible adverse effects and safety risks, to preliminarily evaluate the efficacy of the product for specific targeted diseases and to determine dosage tolerance, optimal dosage and dosing schedule.

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

Post-approval clinical trials, sometimes referred to as Phase 4 clinical trials, may be conducted after initial marketing approval. These clinical trials are used to gain additional experience from the treatment of patients in the intended therapeutic indication, particularly for long-term safety follow-up.

During all phases of clinical development, regulatory agencies require extensive monitoring and auditing of all clinical activities, clinical data, and clinical trial investigators. Annual progress reports detailing the progress of the clinical trials must be submitted to the FDA. Written IND safety reports must be promptly submitted to the FDA, the NIH and the investigators 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 patients, or any clinically important increase in the rate of a serious suspected adverse reaction over that listed in the protocol or investigator brochure. The sponsor must submit an IND safety report within 15 calendar days after the sponsor determines that the information qualifies for reporting. The sponsor also must notify the FDA of any unexpected fatal or life-threatening suspected adverse reaction within seven calendar days after the sponsor's initial receipt of the information. Phase 1, Phase 2 and Phase 3 clinical trials may not be completed successfully within any specified period, if at all. The FDA or the sponsor or its data safety monitoring board may suspend or terminate a clinical trial at any time on various grounds, including a finding that the research patients are being exposed to an unacceptable health risk, including risks inferred from other unrelated immunotherapy trials. 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 biological product has been associated with unexpected serious harm to patients.

Human immunotherapy products are a new category of therapeutics. Because this is a relatively new and expanding area of novel therapeutic interventions, there can be no assurance as to the length of the trial period, the number of patients the FDA will require to be enrolled in the clinical trials in order to establish the safety, efficacy, purity and potency of immunotherapy products, or that the data generated in these clinical trials will be acceptable to the FDA to support marketing approval.

Concurrently with clinical trials, companies usually complete additional studies and must also develop additional information about the physical characteristics of the biological product as well as finalize a process for manufacturing the product in commercial quantities in accordance with cGMP requirements. To help reduce the risk of the introduction of adventitious agents with use of biological products, the PHSA emphasizes the importance of manufacturing control for products whose attributes cannot be precisely defined. The manufacturing process must be capable of consistently producing quality batches of the product candidate and, among other things, the sponsor must develop methods for testing the identity, strength, quality, potency and purity of the final biological product. Additionally, appropriate packaging must be selected and tested and stability studies must be conducted to demonstrate that the biological product candidate does not undergo unacceptable deterioration over its shelf life.

Federal law requires that we register all of our clinical trials on a publicly accessible website. We must also provide results information for most of our clinical trials, other than Phase 1 clinical trials.

#### U.S. Review and Approval Processes

After the completion of clinical trials of a biological product, FDA approval of a BLA must be obtained before commercial marketing of the biological product. The BLA must include results of product development, laboratory and animal studies, human trials, information on the manufacture and composition of the product, proposed labeling and other relevant information. The FDA may grant deferrals for submission of certain data or full or partial waivers. The testing and approval processes require substantial time and effort and 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.

Under the Prescription Drug User Fee Act, or PDUFA, as amended, each BLA must be accompanied by a significant user fee. The FDA adjusts the PDUFA user fees on an annual basis. PDUFA also imposes an annual product fee for biological products and an annual establishment fee on facilities used to manufacture prescription biological products. Fee waivers or reductions are available in certain circumstances, including a waiver of the application fee for the first application filed by a small business. Additionally, no user fees are assessed on BLAs for products designated as orphan drugs, unless the application also includes a non-orphan indication.

Within 60 days following submission of the application, the FDA reviews a BLA submitted 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. Once the submission is accepted for filing, the FDA begins an in-depth substantive review of the BLA. The FDA reviews the BLA to determine, among other things, whether the proposed product is safe, potent, and/or effective for its intended use, and has an acceptable purity profile, and whether the product is being manufactured in accordance with cGMP to assure and preserve the product's identity, safety, strength, quality, potency and purity. The FDA may refer applications for novel biological products or biological products that present difficult questions of safety or efficacy to an advisory committee, typically a panel that includes clinicians and other experts, for review, evaluation and a recommendation as to whether the application should be approved and under what conditions. The FDA is not bound by the recommendations of an advisory committee, but it considers such recommendations carefully when making decisions. During the biological product approval process, the FDA also will determine whether a Risk Evaluation and Mitigation Strategy, or REMS, is necessary to assure the safe use of the biological product. If the FDA concludes a REMS is needed, the sponsor of the BLA must submit a proposed REMS. The FDA will not approve a BLA without a REMS, if required.

Before approving a BLA, the FDA will inspect the facilities at which the product is manufactured. The FDA will not approve the product 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. For immunotherapy products, the FDA also will not approve the product if the manufacturer is not in compliance with the GTPs, to the extent applicable. These are FDA regulations and guidance documents that govern the methods used in, and the facilities and controls used for, the manufacture of HCT/Ps. The primary intent of the GTP requirements is to ensure that cell and tissue based products are manufactured in a manner designed to prevent the introduction, transmission and spread of communicable disease. FDA regulations also require HCT/P establishments to register and list their HCT/Ps with the FDA and, when applicable, to evaluate donors through screening and testing. Additionally, before approving a BLA, the FDA will typically inspect one or more clinical sites to assure that the clinical trials were conducted in compliance with IND trial requirements and GCP requirements. To maintain compliance with cGMPs, GTPs, and GCPs, an applicant must incur significant expenditure of time, money and effort in the areas of training, record keeping, production, and quality control.

Notwithstanding the submission of relevant data and information, the FDA may ultimately decide that the BLA does not satisfy its regulatory criteria for approval and deny approval. Data obtained from clinical trials are not always conclusive and the FDA may interpret data differently than we interpret the same data. If the agency decides not to approve the BLA in its present form, the FDA will issue a complete response letter that describes all of the specific deficiencies in the BLA identified by the FDA. The deficiencies identified may be minor, for example, requiring labeling changes, or major, for example, requiring additional clinical trials. Additionally, the complete response letter may include recommended actions that the applicant might take to place the application in a condition for approval. If a complete response letter is issued, the applicant may either resubmit the BLA, addressing all of the deficiencies identified in the letter, or withdraw the application.

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. The FDA may impose restrictions and conditions on product distribution, prescribing, or dispensing in the form of a REMS or other risk management plan, or otherwise limit the scope of any approval. In addition, the FDA may require post marketing clinical trials, sometimes referred to as Phase 4 clinical trials, designed to further assess a biological product's safety and effectiveness, and testing and surveillance programs to monitor the safety of approved products that have been commercialized.

In addition, under the Pediatric Research Equity Act, or PREA, a BLA or supplement to a BLA must contain data to assess the safety and effectiveness of the product for the claimed indications in all relevant pediatric subpopulations and to support dosing and administration for each pediatric subpopulation for which the product is safe and effective. The FDA may grant deferrals for submission of data or full or partial waivers. Unless otherwise required by regulation, PREA does not apply to any product for an indication for which orphan designation has been granted. However, if only one indication for a product has orphan designation, a pediatric assessment may still be required for any applications to market that same product for the non-orphan indication(s). Sponsors in satisfaction of this obligation may receive an additional six months of marketing exclusivity for all dosage forms and all indications with the same active moiety as the drug studied.

#### 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 generally a disease or condition that affects fewer than 200,000 individuals in the United States, or more than 200,000 individuals in the United States and for which there is no reasonable expectation that the cost of developing and making available in the United States a drug or biologic for this type of disease or condition will be recovered from sales in the United States for that drug or biologic. Orphan drug designation must be

requested before submitting a BLA. After the FDA grants orphan drug 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 shorten the duration of the regulatory review or approval process, but does provide certain advantages, such as a waiver of PDUFA fees, enhanced access to FDA staff, and potential waiver of PREA requirements discussed above.

If a product that has orphan drug designation subsequently receives the first FDA approval for the disease for which it has such designation, the product is entitled to orphan product exclusivity, which means that the FDA may not approve any other applications, including a full BLA, to market the same biologic for the same indication for seven years, except in limited circumstances, such as a showing of clinical superiority to the product with orphan drug exclusivity. Orphan drug 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 user fee.

A designated orphan drug may not receive orphan drug 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 United States 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.

We are currently in discussions with FDA regarding orphan drug designation for our investigational products.

#### Expedited Development and Review Programs

The FDA has a Fast Track program that is intended to expedite or facilitate the process for reviewing new products that meet certain criteria. Specifically, new products are eligible for Fast Track designation if they are intended to treat a serious or life-threatening disease or condition and demonstrate the potential to address unmet medical needs, or if the drug has been designated as a qualified infectious disease product. Fast Track designation applies to the combination of the product and the specific indication for which it is being studied. Under Fast Track, the FDA may consider for review sections of the BLA on a rolling basis before the complete application is submitted, if the sponsor provides a schedule for the submission of the sections of the BLA, the FDA agrees to accept sections of the BLA and determines that the schedule is acceptable, and the sponsor pays any required user fees upon submission of the first section of the BLA. Even if Fast Track designation is granted, it may be rescinded if the product no longer meets the qualifying criteria.

Any product, submitted to the FDA for approval, including a product with a Fast Track designation, may also be eligible for other types of FDA programs intended to expedite development and review, such as priority review and accelerated approval. A product is eligible for priority review if it treats a serious condition and, if approved, would provide a significant improvement in safety and effective. The FDA will attempt to direct additional resources to the evaluation of an application for a new product designated for priority review in an effort to facilitate the review. Additionally, a product may be eligible for accelerated approval. Products studied for their safety and effectiveness in treating serious or life-threatening diseases or conditions may receive accelerated approval upon a determination that the product treats a serious condition, provides a meaningful advantage over available therapies, and demonstrates an effect on a surrogate endpoint that is reasonably likely to predict clinical benefit, or on a clinical endpoint that can be measured earlier than irreversible morbidity or mortality, that is reasonably likely to predict an effect on irreversible morbidity or mortality or other clinical benefit, taking into account the severity, rarity, or prevalence of the condition and the availability or lack of alternative treatments. As a condition of approval, the FDA may require that a sponsor of a drug or biological product receiving accelerated approval perform appropriate post-marketing clinical studies to verify and describe the predicted effect on irreversible morbidity or mortality or other clinical benefit. In addition, the FDA currently requires as a condition for accelerated approval pre-approval of promotional materials, which could adversely impact the timing of the commercial launch of the product. The FDCA also provides expedited procedures for FDA withdrawal of approval of a product approved through accelerated approval. Fast Track designation, priority review and accelerated approval do not change the standards for approval but may expedite the development or approval process.

In 2012 the FDA established a Breakthrough Therapy Designation which is intended to expedite the development and review of products that treat serious or life-threatening conditions. The designation requires preliminary clinical evidence that may demonstrate substantial improvement on a clinically significant endpoint over available therapies. The designation includes all of the Fast Track program features, as well as more intensive FDA interaction and guidance, organizational commitment, and other potential actions to expedite review. The Breakthrough Therapy Designation is a distinct status from both accelerated approval and priority review, which can also be granted to the same product if relevant criteria are met. If a product is designated as breakthrough therapy, FDA will expedite the development and review of such product. Even if a Breakthrough Therapy Designation is granted, it may be rescinded if the product no longer meets the qualifying criteria.

Where applicable, we plan to request Fast Track and Breakthrough Therapy Designation for our product candidates, including BPX-051, BPX-401 and BPX-601. Even if we receive one or both of these designations for our product candidates, the FDA may later decide that our product candidates no longer meets the conditions for qualification. In addition, these designations may not provide us with a material commercial advantage.

#### Post-Approval Requirements



Any product for which we receive FDA approval is 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, which include, among others, standards for direct-to-consumer advertising, restrictions on promoting products for uses or in patient populations that are not described in the product's approved uses (known as "off-label use"), limitations on industry-sponsored scientific and educational activities, and requirements for promotional activities involving the internet. Although physicians may prescribe legally available products for off-label uses, if the physicians deem it to be appropriate in their professional medical judgment, manufacturers may not market or promote such off-label uses.

In addition, quality control and manufacturing procedures must continue to conform to applicable manufacturing requirements after approval to ensure the long-term stability of the product. We rely, and expect to continue to rely, on third parties for the production of clinical and commercial quantities of our products in accordance with cGMP regulations. cGMP regulations require among other

things, quality control and quality assurance as well as the corresponding maintenance of records and documentation and the obligation to investigate and correct any deviations from cGMP. Manufacturers and other entities involved in the manufacture and distribution of approved products are required to register their establishments with the FDA and certain state agencies, and are subject to periodic unannounced inspections by the FDA and certain state agencies for compliance with cGMP and other laws. Accordingly, manufacturers must continue to expend time, money, and effort in the area of production and quality control to maintain cGMP compliance. Discovery of problems with a product after approval may result in restrictions on a product, manufacturer, or holder of an approved BLA, including, among other things, recall or withdrawal of the product from the market, seizure of product manufactured not in accordance with GMPs, suspension or termination of manufacturing activities at one or more facilities, or other civil or criminal sanctions. In addition, changes to the manufacturing process are strictly regulated, and depending on the significance of the change, may require prior FDA approval before being implemented. Other types of changes to the approved product, such as adding new indications and claims, are also subject to further FDA review and approval.

The FDA also may require post-marketing testing, known as Phase 4 testing, and surveillance to monitor the effects of an approved product. Discovery of previously unknown problems with a product or the failure to comply with applicable FDA requirements can have negative consequences, including adverse publicity, judicial or administrative enforcement, warning letters from the FDA, mandated corrective advertising or communications with doctors, and civil or criminal penalties, among others. Newly discovered or developed safety or effectiveness data may require changes to a product's approved labeling, including the addition of new warnings and contraindications, and also may require the implementation of a REMS or other risk management measures. Also, new government requirements, including those resulting from new legislation, may be established, or the FDA's policies may change, which could delay or prevent regulatory approval of our products under development.

#### U.S. Patent Term Restoration and Marketing Exclusivity

The Biologics Price Competition and Innovation Act, or BPCIA, amended the PHSA to authorize the FDA to approve similar versions of innovative biologics, commonly known as biosimilars. Among other requirements, a competitor seeking approval of a biosimilar must file an application to establish its molecule as highly similar to an approved innovator biologic, without any clinically meaningful differences in terms of safety, purity, and potency. The BPCIA, however, bars the FDA from approving biosimilar applications for 12 years after an innovator biological product receives initial marketing approval. This 12-year period of data exclusivity may be extended by six months, for a total of 12.5 years, if the FDA requests that the innovator company conduct pediatric clinical investigations of the product. Although a statutory provision exists for FDA approval of biosimilars, FDA has yet to provide clarity on many aspects of the regulatory pathway for such products. Furthermore, the first biosimilar applications have only recently been submitted to FDA, and it remains to be seen how FDA will apply the statutory biosimilar provisions to biological products such as ours.

Depending upon the timing, duration and specifics of the FDA approval of the use of our product candidates, some of our U.S. patents, if granted, may be eligible for limited patent term extension under the Drug Price Competition and Patent Term Restoration Act of 1984, commonly referred to as the Hatch-Waxman Act. The Hatch-Waxman Act permits a patent restoration term of up to five years, as compensation for patent term lost during product development and the FDA regulatory review process. However, patent term restoration cannot extend the remaining term of a patent beyond a total of 14 years from the product's approval date. The patent term restoration period is generally one-half the time between the effective date of an IND and the submission date of a BLA plus the time between the submission date of a BLA and the approval of that application. Only one patent applicable to an approved product is eligible for the extension and the application for the extension must be submitted prior to the expiration of the patent. The 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 may intend to apply for restoration of patent term for one of our currently owned or licensed patents to add patent life beyond its current expiration date, depending on the expected length of the clinical trials and other factors involved in the filing of the relevant BLA.

Other U.S. Healthcare Laws and Compliance Requirements

In the United States, our activities are potentially subject to regulation by various federal, state and local authorities in addition to the FDA, including but not limited to, the Centers for Medicare and Medicaid Services, or CMS, other divisions of the U.S. Department of Health and Human Services (e.g., the Office of Inspector General), the U.S. Department of Justice, or DOJ, and individual U.S. Attorney offices within the DOJ, and state and local governments. For example, sales, marketing and scientific/educational grant programs must comply with the anti-fraud and abuse provisions of the Social Security Act, the false claims laws, the privacy provisions of the Health Insurance Portability and Accountability Act, or HIPAA, the sunshine provisions of the Affordable Care Act, and similar state laws, each as amended.

The federal Anti-Kickback Statute prohibits, among other things, any person or entity, from knowingly and willfully offering, paying, soliciting or receiving any remuneration, directly or indirectly, overtly or covertly, in cash or in kind, to induce or in return for purchasing, leasing, ordering or arranging for the purchase, lease or order of any good, facility, item or service reimbursable, in whole

or in part, under Medicare, Medicaid or other federal healthcare programs. The term remuneration has been interpreted broadly to include anything of value. The Anti-Kickback Statute has been interpreted to apply to arrangements between biologic manufacturers on one hand and prescribers, purchasers, and formulary managers on the other. There are a number of statutory exceptions and regulatory safe harbors protecting some common activities from prosecution. The exceptions and safe harbors are drawn narrowly and practices that involve remuneration that may be alleged to be intended to induce prescribing, purchasing or recommending may be subject to scrutiny if they do not qualify for an exception or safe harbor. Failure to meet all of the requirements of a particular applicable statutory exception or regulatory safe harbor does not make the conduct per se illegal under the Anti-Kickback Statute. Instead, the legality of the arrangement will be evaluated on a case-by-case basis based on a cumulative review of all of its facts and circumstances.

Additionally, the intent standard under the Anti-Kickback Statute was amended by the Affordable Care Act to a stricter standard such that a person or entity no longer needs to have actual knowledge of the statute or specific intent to violate it in order to have committed a violation. In addition, the Affordable Care Act codified case law that a claim including items or services resulting from a violation of the federal Anti-Kickback Statute constitutes a false or fraudulent claim for purposes of the federal civil False Claims Act.

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

The federal false claims laws, including but not limited to the federal civil False Claims Act, prohibit, among other things, any person or entity from knowingly presenting, or causing to be presented, a false claim for payment to, or approval by, the federal government. Pharmaceutical and other healthcare companies have been prosecuted under these laws for allegedly providing free product to customers with the expectation that the customers would bill federal programs for the product. Other companies have been prosecuted for causing false claims to be submitted because of the companies' marketing of the product for unapproved (i.e., off-label), and thus non-reimbursable, uses.

HIPAA created new federal criminal statutes that prohibit knowingly and willfully executing, or attempting to execute, a scheme to defraud or to obtain, by means of false or fraudulent pretenses, representations or promises, any money or property owned by, or under the control or custody of, any healthcare benefit program, including private third-party payors and knowingly and willfully falsifying, concealing or covering up by trick, scheme or device, a material fact or making any materially false, fictitious or fraudulent statement in connection with the delivery of or payment for healthcare benefits, items or services.

Also, many states have similar fraud and abuse statutes or regulations that apply to items and services reimbursed under Medicaid and other state programs, or, in several states, apply regardless of the payor.

We may be subject to data privacy and security regulations by both the federal government and the states in which we conduct our business. HIPAA, as amended by the Health Information Technology for Economic and Clinical Health Act, or HITECH, and its implementing regulations, imposes requirements relating to the privacy, security and transmission of individually identifiable health information. Among other things, HITECH makes HIPAA's security standards directly applicable to business associates independent contractors or agents of covered entities that receive or obtain protected health information in connection with providing a service on behalf of a covered entity. HITECH also created four new tiers of civil monetary penalties, amended HIPAA to make civil and criminal penalties directly applicable to business associates, and gave state attorneys general new authority to file civil actions for damages or injunctions in federal courts to enforce the federal HIPAA laws and seek attorneys' fees and costs associated with pursuing federal civil actions. In addition, state laws govern the privacy and security of health information in specified circumstances, many of which differ from each other in significant ways and may not have the same effect, thus complicating compliance efforts.

Additionally, the federal Physician Payments Sunshine Act within the Affordable Care Act, and its implementing regulations, require that certain manufacturers of drugs, devices, biological and medical supplies for which payment is available under Medicare, Medicaid or the Children's Health Insurance Program (with certain exceptions) to report annually information related to certain payments or other transfers of value made or distributed to physicians and teaching hospitals, or to entities or individuals at the request of, or designated on behalf of, the physicians and teaching hospitals and to report annually certain ownership and investment interests held by physicians and their immediate family members.

We will also be required to begin satisfying the product tracing, verification, and reporting requirements set out in the newly enacted Drug Quality and Security Act.

In order to distribute products commercially, we must also comply with state laws that require the registration of manufacturers and wholesale distributors of drug and biological products in a state, including, in certain states, manufacturers and distributors who ship products into the state even if such manufacturers or distributors have no place of business within the state.

Several states have enacted legislation requiring pharmaceutical and biotechnology companies to, among other things, establish marketing compliance programs, file periodic reports with the state, make periodic public disclosures on sales, marketing, pricing, clinical trials and other activities, and/or register their sales representatives, as well as to prohibit pharmacies and other healthcare entities from providing certain physician prescribing data to pharmaceutical and biotechnology companies for use in sales and marketing, and to prohibit certain other sales and marketing practices. All of our activities are potentially subject to federal and state consumer protection and unfair competition laws.

If our operations are found to be in violation of any of the federal and state healthcare laws described above or any other governmental regulations that apply to us, we may be subject to penalties, including without limitation, civil, criminal and/or administrative penalties, damages, fines, disgorgement, exclusion from participation in government programs, such as Medicare and Medicaid, injunctions, private “qui tam” actions brought by individual whistleblowers in the name of the government, or refusal to allow us to enter into government contracts, contractual damages, reputational harm, administrative burdens, diminished profits and future earnings, and the curtailment or restructuring of our operations, any of which could adversely affect our ability to operate our business and our results of operations.

### Coverage, Pricing and Reimbursement

Significant uncertainty exists as to the coverage and reimbursement status of any product candidates for which we obtain regulatory approval. In the United States and markets in other countries, sales of any products for which we receive regulatory approval for commercial sale will depend, in part, on the extent to which third-party payors provide coverage and establish adequate reimbursement levels for such products. In the United States, third-party payors include federal and state healthcare programs, private managed care providers, health insurers and other organizations. The process for determining whether a third-party payor will provide coverage for a product may be separate from the process for setting the price of a product or for establishing the reimbursement rate that such a payor will pay for the product. Third-party payors may limit coverage to specific products on an approved list, also known as a formulary, which might not include all of the FDA-approved products for a particular indication. Third-party payors are increasingly challenging the price, examining the medical necessity and reviewing the cost-effectiveness of medical products, therapies and services, in addition to questioning their safety and efficacy. We may need to conduct expensive pharmaco-economic studies in order to demonstrate the medical necessity and cost-effectiveness of our products, in addition to the costs required to obtain the FDA approvals. Our product candidates may not be considered medically necessary or cost-effective. A payor’s decision to provide coverage for a product does not imply that an adequate reimbursement rate will be approved. Further, one payor’s determination to provide coverage for a product does not assure that other payors will also provide coverage for the product. Adequate third-party reimbursement may not be available to enable us to maintain price levels sufficient to realize an appropriate return on our investment in product development.

Different pricing and reimbursement schemes exist in other countries. In the EU, governments influence the price of pharmaceutical products through their pricing and reimbursement rules and control of national health care systems that fund a large part of the cost of those products to consumers. Some jurisdictions operate positive and negative list systems under which products may only be marketed once a reimbursement price has been agreed. To obtain reimbursement or pricing approval, some of these countries may require the completion of clinical trials that compare the cost-effectiveness of a particular product candidate to currently available therapies. Other member states allow companies to fix their own prices for medicines, but monitor and control company profits. The downward pressure on health care costs has become very intense. As a result, increasingly high barriers are being erected to the entry of new products. In addition, in some countries, cross-border imports from low-priced markets exert a commercial pressure on pricing within a country.

The marketability of any product candidates for which we receive regulatory approval for commercial sale may suffer if the government and third-party payors fail to provide adequate coverage and reimbursement. In addition, emphasis on managed care in the United States has increased and we expect will continue to increase the pressure on healthcare

pricing. Coverage policies and third-party reimbursement rates may change at any time. Even if favorable coverage and reimbursement status is attained for one or more products for which we receive regulatory approval, less favorable coverage policies and reimbursement rates may be implemented in the future.

#### Healthcare Reform

In March 2010, President Obama signed the Affordable Care Act, which has the potential to substantially change healthcare financing and delivery by both governmental and private insurers, and significantly impact the pharmaceutical and biotechnology industry. The Affordable Care Act will impact existing government healthcare programs and will result in the development of new programs.

Among the Affordable Care Act's provisions of importance to the pharmaceutical and biotechnology industries, in addition to those otherwise described above, are the following:

- an annual, nondeductible fee on any entity that manufactures or imports certain specified branded prescription drugs and biologic agents apportioned among these entities according to their market share in some government healthcare programs, that began in 2011;
- an increase in the statutory minimum rebates a manufacturer must pay under the Medicaid Drug Rebate Program, retroactive to January 1, 2010, to 23.1% and 13% of the average manufacturer price for most branded and generic drugs, respectively and capped the total rebate amount for innovator drugs at 100% of the Average Manufacturer Price, or AMP;
- a new Medicare Part D coverage gap discount program, in which manufacturers must agree to offer 50% point-of-sale discounts off negotiated prices of applicable brand drugs to eligible beneficiaries during their coverage gap period, as a condition for the manufacturers' 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;
- expansion of eligibility criteria for Medicaid programs by, among other things, allowing states to offer Medicaid coverage to additional individuals with income at or below 133% of the federal poverty level, thereby potentially increasing manufacturers' Medicaid rebate liability;
- expansion of the entities eligible for discounts under the Public Health Service pharmaceutical pricing program; 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.

We anticipate that the Affordable Care Act will result in additional downward pressure on coverage and the price that we receive for any approved product, and could seriously harm our business. Any reduction in reimbursement from Medicare and other government programs may result in a similar reduction in payments from private payors. The implementation of cost containment measures or other healthcare reforms may prevent us from being able to generate revenue, attain profitability, or commercialize our products.

There have also been changes to the reimbursement landscape in the U.S. since the passage of the Affordable Care Act. On August 2, 2011, the President signed into law the Budget Control Act of 2011, which, among other things, created the Joint Select Committee on Deficit Reduction to recommend to Congress proposals in spending reductions. The Joint Select Committee did not achieve a targeted deficit reduction of at least \$1.2 trillion for the years 2013 through 2021, triggering the legislation's automatic reduction to several government programs. This includes reductions to Medicare payments to providers of 2% per fiscal year, which went into effect on April 1, 2013 and will stay in effect through 2024 unless additional Congressional action is taken. On January 2, 2013, President Obama signed into law the American Taxpayer Relief Act of 2012, which, among other things, reduced Medicare payments to several providers, including hospitals, imaging centers and cancer treatment centers and increased the statute of limitations period for the government to recover overpayments to providers from three to five years. We expect that additional state and federal healthcare reform measures will be adopted in the future, any of which could limit the amounts that federal and state governments will pay for healthcare products and services, which could result in reduced demand for our products and/or additional pricing pressure. In addition, it is possible that there will be further legislation or regulation that could harm our business, financial condition, and results of operations.

#### The Foreign Corrupt Practices Act

The Foreign Corrupt Practices Act, or FCPA, prohibits any U.S. individual or business from paying, offering, or authorizing payment or offering of anything of value, directly or indirectly, to any foreign official, political party or candidate for the purpose of influencing any act or decision of the foreign entity in order to assist the individual or business in obtaining or retaining business. The FCPA also obligates companies whose securities are listed in the United States to comply with accounting provisions requiring the company to maintain books and records that accurately and fairly reflect all transactions of the corporation, including international subsidiaries, and to devise and maintain an adequate system of internal accounting controls for international operations.





### Additional Regulation

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

### Europe / Rest of World Government Regulation

In addition to regulations in the United States, we will be subject to a variety of regulations in other jurisdictions governing, among other things, clinical trials and any commercial sales and distribution of our products. Whether or not we obtain FDA approval of a product, we must obtain the requisite approvals from regulatory authorities in foreign countries prior to the commencement of clinical trials or marketing of the product in those countries. Certain countries outside of the United States have a similar process that requires the submission of a clinical trial application much like the IND prior to the commencement of human clinical trials. In the EU, for example, a clinical trial application must be submitted to each country's national health authority and an independent ethics committee, much like the FDA and IRB, respectively. Once the clinical trial application is approved in accordance with a country's requirements, clinical trial development may proceed. Because biologically sourced raw materials are subject to unique contamination risks, their use may be restricted in some countries. The requirements and process governing the conduct of clinical trials, product licensing, pricing and reimbursement vary from country to country. In all cases, the clinical trials are conducted in accordance with GCP and the applicable regulatory requirements and the ethical principles that have their origin in the Declaration of Helsinki.

To obtain regulatory approval of an investigational drug or biological product under EU regulatory systems, we must submit a marketing authorization application. The application used to file the BLA in the United States is similar to that required in the EU, with the exception of, among other things, country-specific document requirements.

For other countries outside of the EU, such as countries in Eastern Europe, Latin America or Asia, the requirements governing the conduct of clinical trials, product licensing, pricing and reimbursement vary from country to country. In all cases, again, the clinical trials are conducted in accordance with GCP and the applicable regulatory requirements and the ethical principles that have their origin in the Declaration of Helsinki.

### Employees

As of December 31, 2014, we had 35 employees, all of whom were full-time, 27 of whom were engaged in research and development activities and 8 of whom were engaged in business development, finance, information systems, facilities, human resources or administrative support. None of our employees is subject to a collective bargaining agreement. We consider our relationship with our employees to be good.

### Corporate Information

We were incorporated in Delaware in July 2004. Our principal executive offices are located at 2130 W. Holcombe Blvd., Ste. 800, Houston, Texas and our telephone number is (832) 384-1100. Our corporate website address is [www.bellicum.com](http://www.bellicum.com). Our Annual Report on Form 10-K, Quarterly Reports on Form 10-Q, Current Reports on Form 8-K, and amendments to reports filed pursuant to Sections 13(a) and 15(d) of the Securities Exchange Act of 1934, as amended, or the Exchange Act, will be made available free of charge on our website as soon as reasonably practicable after we electronically file such material with, or furnish it to, the Securities and Exchange Commission, or

the SEC. The contents of our website are not incorporated into this Annual Report and our reference to the URL for our website is intended to be an inactive textual reference only.

We are an “emerging growth company,” as defined in the JOBS Act. We will remain an emerging growth company until the earlier of (1) the last day of the fiscal year (a) following the fifth anniversary of the completion of our initial public offering in December 2014, (b) in which we have total annual gross revenue of at least \$1.0 billion, or (c) in which we are deemed to be a large accelerated filer, which means the market value of our common stock that is held by non-affiliates exceeded \$700.0 million as of the prior June 30th, and (2) the date on which we have issued more than \$1.0 billion in non-convertible debt during the prior three-year period. References to “emerging growth company” in this Annual Report on Form 10-K have the meaning associated with it in the JOBS Act.

## ITEM 1A. Risk Factors

You should carefully consider the following risk factors, as well as the other information in this report, and in our other public filings. The occurrence of any of the following 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 in this report and those we may make from time to time. You should consider all of the risk factors described when evaluating our business.

### Risks Related to Our Business and Industry

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

We are a clinical stage biopharmaceutical company with a limited operating history. We are not profitable and have incurred losses in each period since our inception in 2004. To date, we have financed our operations primarily through equity and debt financings. For the years ended December 31, 2014 and 2013, we reported a net loss of \$84.0 million and \$8.0 million, respectively. As of December 31, 2014, we had an accumulated deficit of \$112.9 million. We expect to continue to incur significant losses for the foreseeable future, and we expect these losses to increase as we continue our research and development of, and seek regulatory approvals for, our product candidates.

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

Biopharmaceutical product development is a highly speculative undertaking and involves a substantial degree of uncertainty. We have never generated any revenue from product sales and may never be profitable.

We have devoted substantially all of our financial resources and efforts to developing our proprietary CID technology platform, identifying potential product candidates and conducting preclinical studies and clinical trials. We are still in the early stages of developing our product candidates, and we have not completed development of any products. Our ability to generate revenue and achieve profitability depends in large part on our ability, alone or with partners, to successfully complete the development of, obtain the necessary regulatory approvals for, and commercialize, product candidates. We do not anticipate generating revenues from sales of products for the foreseeable future. Our ability to generate future revenues from product sales depends heavily on our success in:

- completing clinical trials through all phases of clinical development of our current product candidates, as well as the product candidates that are being developed by our partners and licensees;
- seeking and obtaining marketing approvals for product candidates that successfully complete clinical trials;
- launching and commercializing product candidates for which we obtain marketing approval, with a partner or, if launched independently, successfully establishing a sales force, marketing and distribution infrastructure;
- identifying and developing new product candidates;
- progressing our pre-clinical programs into human clinical trials;
- establishing and maintaining supply and manufacturing relationships with third parties;
- developing new molecular switches based on our proprietary CID technology platform;
- maintaining, protecting, expanding and enforcing our intellectual property; and
- attracting, hiring and retaining qualified personnel.

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

ever. In addition, our expenses could increase beyond expectations if we are required by the FDA, or foreign regulatory agencies, to perform studies and clinical trials in addition to those that we currently anticipate, or if there are any delays in our or our partners completing clinical trials or the development of any of our product candidates. If one or more of the product candidates that we independently develop is approved for commercial sale, we anticipate incurring significant costs associated with commercializing such product candidates. Even if we or our partners are able to generate revenues from the sale of any approved products, we may not become profitable and may need to obtain additional funding to continue operations, which may not be available to us on favorable terms, if at all. Even if we do achieve profitability, we may not be able to sustain or increase profitability on a quarterly or annual basis. Our failure to become and remain profitable would depress the value of our company and could impair our ability to raise capital, expand our business, maintain our research and development efforts, diversify our product offerings or even continue our operations. A decline in the value of our company could also cause stockholders to lose all or part of their investment.

We have concentrated our therapeutic product research and development efforts on our CID platform, and our future success depends on the successful development of this therapeutic approach.

Our proprietary CID technology platform is novel and there are no approved products or product candidates in late-stage clinical trials based on this technology. Additionally, the safety and efficacy profile of rimiducid has not been subject to large scale clinical testing. If rimiducid is found to have a poor safety profile in clinical trials, or if our technology is not effective, we may be required to redesign all of our product candidates, which would require significant time and expense. In addition, our CID platform technology may not be applicable or effective in the development of additional cellular immunotherapies beyond our current programs which would adversely affect our business and prospects.

CAR T cell therapies are novel and present significant challenges.

CAR-T and TCR product candidates represent a relatively new field of cellular immunotherapy and there are no FDA-approved products in this area. Advancing this novel and personalized therapy creates significant challenges for us, including:

- obtaining regulatory approval, as the FDA and other regulatory authorities have limited experience with commercial development of T-cell therapies for cancer;
- 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 T 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; and
- establishing sales and marketing capabilities upon obtaining any regulatory approval to gain market acceptance of a novel therapy.

Our inability to successfully develop CAR-T and TCR cell therapies or develop processes related to the manufacture, sales and marketing of these therapies would adversely affect our business, results of operations and prospects. We believe that we have appropriately accounted for the above factors while pursuing the development and commercialization of our product candidates, but we cannot entirely eliminate the risks associated with novel technology.

Failure to successfully develop and obtain approval of our lead product candidate BPX-501 or our other clinical product candidates could adversely affect our future success.

Our business and future success depends, in part, on our ability to obtain regulatory approval of and then successfully commercialize our lead product candidate, BPX-501 and our other clinical product candidates. BPX-501 is in the early stages of development. All of our product candidates, including BPX-501, will require additional clinical and non-clinical development, regulatory review and approval in multiple jurisdictions, substantial investment, and access to sufficient commercial manufacturing capacity and significant marketing efforts before we can generate any revenue from product sales. In addition, because BPX-501 is our most advanced product candidate, and because many of our other product candidates are based on similar technology, if BPX-501 encounters safety or efficacy problems, developmental delays or regulatory issues or other problems, our development plans and business for our other product candidates would be significantly harmed. In addition, our product candidates that incorporate the CID “safety switch” combine genetically modified T cells that are used to enhance the patients’ immune system and a small molecule that leads to the death of these modified T cells if they cause safety issues.

Our clinical trials may fail to adequately demonstrate the safety and efficacy of any of our product candidates, which would prevent or delay regulatory approval and commercialization.

Before obtaining regulatory approvals for the commercial sale of our product candidates, we must demonstrate through lengthy, complex and expensive preclinical testing and clinical trials that our product candidates are both safe and effective for use in each target indication. Clinical testing is expensive and can take many years to complete, and its outcome is inherently uncertain. Failure can occur at any time during the clinical trial process. The results of preclinical studies and early clinical trials of our product candidates may not be predictive of the results of later-stage clinical trials. We expect there may be greater variability in results for cellular immunotherapy products processed and administered on a patient-by-patient basis, like all of our CID technology-based development and product candidates, than for “off-the-shelf” products, like many drugs. There is typically an extremely high rate of attrition from the failure of product candidates proceeding through clinical trials. Product candidates in later stages of clinical trials may fail to show the desired safety and efficacy profile despite having progressed through preclinical studies and initial clinical trials. A number of companies in the biopharmaceutical industry have suffered significant setbacks in advanced clinical trials due to lack of

efficacy or unacceptable safety issues, notwithstanding promising results in earlier clinical trials. Most product candidates that commence clinical trials are never approved as products.

We have not completed any clinical studies of our current product candidates. Success in early clinical studies may not be indicative of results obtained in later studies.

Many of our current product candidates have not initiated evaluation in human clinical studies, and we may experience unexpected results in the future. Differences in cell processing, time of administration and patient conditioning, among other factors, may result in our experiencing different results in our clinical trials from those reported in trials by our collaborators, and may mean that we experience different results in our clinical trials. In addition, data from preclinical studies and investigator-led Phase 1 or Phase 1/2 clinical trials of BPX-501 therapy should not be relied upon as evidence that later or later-scale clinical trials will succeed. We have designed our planned Phase 1/2 clinical trials of BPX-501 primarily to assess safety and efficacy in a small number of patients with malignant disease or inherited blood disorders. In addition, we are initiating additional Phase 1 and Phase 1/2 clinical trials of BPX-501 and there are a number of investigator-led clinical trials of BPX-501 ongoing and planned.

Similarly, results from preclinical studies, such as in vitro and in vivo studies, of BPX-401, BPX-601, BPX-701 and our other preclinical programs may not be indicative of the results of clinical trials of these product candidates. Furthermore, we may not be able to commence human clinical trials on any of our preclinical product candidates on the time frames we expect. Our failure to meet these expected targets would likely have an adverse effect on our stock price.

Even if the clinical trials are successfully completed, we cannot guarantee that the FDA or foreign regulatory authorities will interpret the results as we do, and more clinical trials could be required before we submit our product candidates for approval. To the extent that the results of the clinical trials are not satisfactory to the FDA or foreign regulatory authorities for support of a marketing application, approval of our product candidates may be significantly delayed, or we may be required to expend significant additional resources, which may not be available to us, to conduct additional clinical trials in support of potential approval of our product candidates.

We may not be successful in our efforts to use and expand our CID platform to build a pipeline of product candidates and develop marketable products.

We believe that our CID platform, which serves as the foundation of our CaspaCIDE, CIDE CAR, GoCAR-T and DeCIDE technologies, can be further leveraged to discover other novel technologies, therapeutic applications and market opportunities. For example, we are currently conducting research in applying our platform TCR therapies for solid tumors, where immune toxicities associated with treatment are even more severe than CAR-T therapies. We are also developing new molecular switches and two-switch systems to provide greater control over cellular immunotherapy. We are at a very early stage of development and our platform has not yet, and may never lead to, approved or marketable products. Even if we are successful in continuing to build our pipeline, the potential product candidates that we identify may not be suitable for clinical development, including for reasons related to their harmful side effects, limited efficacy or other characteristics that indicate that they are unlikely to be products that will receive marketing approval and achieve market acceptance. If we do not successfully develop and commercialize product candidates based upon our technological approach, we may not be able to obtain product or partnership revenues in future periods, which would adversely affect our business, prospects, financial condition and results of operations.

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

We depend and will continue to depend upon independent investigators and collaborators, such as universities, medical institutions, and strategic partners to conduct our preclinical and clinical trials under agreements with us.



Negotiations of budgets and contracts with study sites may result in delays to our development timelines and increased costs. We will rely heavily on these third parties over the course of our clinical trials, and we control only certain aspects of their activities. Nevertheless, we are responsible for ensuring that each of our studies is conducted in accordance with applicable protocol, legal, regulatory and scientific standards, and our reliance on third parties does not relieve us of our regulatory responsibilities. We and these third parties are required to comply with current good clinical practices, or cGCPs, which are regulations and guidelines enforced by the FDA and comparable foreign regulatory authorities for product candidates in clinical development. Regulatory authorities enforce these cGCPs through periodic inspections of clinical trial sponsors, principal investigators and clinical trial sites. If we or any of these third parties fail to comply with applicable cGCP regulations, the clinical data generated in our clinical trials may be deemed unreliable and the FDA or comparable foreign regulatory authorities may require us to perform additional clinical trials before approving our marketing applications. We cannot assure you that, upon inspection, such regulatory authorities will determine that any of our clinical trials comply with the cGCP regulations. In addition, our clinical trials must be conducted with biologic product produced under current good manufacturing practices, or cGMPs, regulations and will require a large number of test patients. Our failure or any failure by these third parties to

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

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

Switching or adding third parties to conduct our clinical trials involves substantial cost and requires extensive management time and focus. In addition, there is a natural transition period when a new third party commences work. As a result, delays occur, which can materially impact our ability to meet our desired clinical development timelines.

Additionally, we are conducting multiple clinical trials in Europe and may plan additional testing of our technology and product candidates in other foreign jurisdictions. We currently have limited staffing and capabilities in foreign countries, and may not be able to effectively resolve potential disputes with our independent investigators and collaborators.

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

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

- the patient eligibility criteria defined in the protocol;
- the size of the patient population required for analysis of the trial's primary endpoints;
- the proximity of patients to study sites;
- the design of the clinical trial;
- our ability to recruit clinical trial investigators with the appropriate competencies and experience;
- our ability to obtain and maintain patient consents; and
- the risk that patients enrolled in clinical trials will drop out of the clinical trials before completion.

In particular, some of our clinical trials will look to enroll patients with characteristics which are found in a very small population, such as patients with CD19-expressing cancers, such as ALL, CLL and non-Hodgkin's lymphomas, and patients with orphan inherited blood disorders. Our clinical trials will compete with other clinical trials for product candidates that are in the same therapeutic areas as our product candidates, and this competition will reduce the number and types of patients available to us, because some patients who might have opted to enroll in our clinical trials may instead opt to enroll in a trial being conducted by one of our competitors. Since the number of qualified clinical investigators is limited, we expect to conduct some of our clinical trials at the same clinical trial sites that some of our competitors use, which will reduce the number of patients who are available for our clinical trials in these clinical trial sites. Moreover, because our product candidates represent a departure from more commonly used methods for cancer treatment, potential patients and their doctors may be inclined to use conventional therapies, such

as chemotherapy and antibody therapy, rather than enroll patients in any of our future clinical trials. Patients may also be unwilling to participate in our clinical trials because of negative publicity from adverse events in the biotechnology or gene therapy industries.

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

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Any adverse developments that occur during any clinical trials conducted by academic investigators, our collaborators or other entities conducting clinical trials under independent INDs may affect our ability to obtain regulatory approval or commercialize our product candidates.

BPX-501 and certain of our other CaspaCIDE product candidates are being used by third parties in clinical trials for which we are collaborating or in clinical trials which are completely independent of our development program. We have little to no control over the conduct of such clinical trials. If serious adverse events occur during these or any other clinical trials using our product candidates, the FDA and other regulatory authorities may delay, limit or deny approval of our product candidate or require us to conduct additional clinical trials as a condition to marketing approval, which would increase our costs. If we receive FDA approval for BPX-501 or any other CaspaCIDE product candidate and a new and serious safety issue is identified in connection with clinical trials conducted by third parties, the FDA and other regulatory authorities may withdraw their approval of the product or otherwise restrict our ability to market and sell our product. In addition, treating physicians may be less willing to administer our product due to concerns over such adverse events, which would limit our ability to commercialize our product.

Adverse side effects or other safety risks associated with our product candidates could delay or preclude approval, cause us to suspend or discontinue clinical trials, abandon product candidates, limit the commercial profile of an approved label, or result in significant negative consequences following marketing approval, if any.

Undesirable side effects caused by our product candidates could result in the delay, suspension or termination of clinical trials by us, the FDA or other regulatory authorities for a number of reasons. If we elect or are required to delay, suspend or terminate any clinical trial of any product candidates that we develop, the commercial prospects of such product candidates will be harmed and our ability to generate product revenues from any of these product candidates will be delayed or eliminated. Serious adverse events observed in clinical trials could hinder or prevent market acceptance of the product candidate at issue. Any of these occurrences may harm our business, prospects, financial condition and results of operations significantly.

In other clinical trials involving CAR T cells, the most prominent acute toxicities included symptoms thought to be associated with the release of cytokines, such as fever, low blood pressure and kidney dysfunction. Some patients also experienced toxicity of the central nervous system, such as confusion, cranial nerve dysfunction and speech impairment. Adverse events by worst grade and attributed to CAR T cells were severe and life threatening in some patients. The life threatening events were related to kidney dysfunction and toxicities of the central nervous system. Severe and life threatening toxicities occurred mostly in the first two weeks after cell infusion and generally resolved within three weeks. In the past, several patients have also died in clinical trials by others involving CAR T cells.

Clinical trials are expensive, time-consuming and difficult to design and implement.

Human clinical trials are expensive and difficult to design and implement, in part because they are subject to rigorous regulatory requirements. Because our product candidates are based on new technology and engineered on a patient-by-patient basis, we expect that they will require extensive research and development and have substantial manufacturing and processing costs. In addition, costs to treat patients with relapsed/refractory cancer and to treat potential side effects that may result from therapies such as our current and future product candidates can be significant. Accordingly, our clinical trial costs are likely to be significantly higher than for more conventional therapeutic technologies or drug products. In addition, our proposed personalized product candidates involve several complex and costly manufacturing and processing steps, the costs of which will be borne by us. The costs of our clinical trials may increase if the FDA does not agree with our clinical development plans or requires us to conduct additional clinical trials to demonstrate the safety and efficacy of our product candidates.

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

The biopharmaceutical industry is characterized by intense competition and rapid innovation. Our competitors may be able to develop other compounds or drugs that are able to achieve similar or better results. Our potential competitors include major multinational pharmaceutical companies, established biotechnology companies, specialty pharmaceutical companies and universities and other research institutions. Many of our competitors have substantially greater financial, technical and other resources, such as larger research and development staff and experienced marketing and manufacturing organizations and well-established sales forces. Smaller or early-stage companies may also prove to be significant competitors, particularly through collaborative arrangements with large, established companies. Mergers and acquisitions in the biotechnology and pharmaceutical industries may result in even more resources being concentrated in our competitors. Competition may increase further as a result of advances in the commercial applicability of technologies and greater availability of capital for investment in these industries. Our competitors, either alone or with collaborative partners, may succeed in developing, acquiring or licensing on an exclusive basis drug or biologic products that are more effective, safer, more easily commercialized or less costly than our product candidates or may develop proprietary technologies or secure patent protection that we may need for the development of our technologies and products. We believe the key competitive

factors that will affect the development and commercial success of our product candidates are efficacy, safety, tolerability, reliability, convenience of use, price and reimbursement.

Specifically, genetically engineering T cells faces significant competition in both the CAR and TCR technology space from multiple companies, including Adaptimmune Limited, bluebird bio, Inc., Celgene Corporation, Cellectis SA, GlaxoSmithKline plc, Intrexon Corporation, Juno Therapeutics, Inc., Kite Pharma, Inc., Novartis AG, Pfizer Inc. and Ziopharm Oncology. Our lead product candidate, BPX-501, is an adjunct therapy for HSCT with alternative donors that potentially improves stem cell engraftment, accelerates host immune system recovery and treats GvHD. Other companies that we are aware of that are developing product candidates to improve the outcome of HSCT, include Kiadis Pharma Netherlands B.V. and Molecular Medicine S.p.A. . BPX-201, based on our DeCIDE technology, is a dendritic cell-based cancer vaccine for the treatment of metastatic prostate cancer and other solid tumors. Other companies that we are aware of that are focused on developing cancer vaccines, include Advaxis, Inc., Argos Therapeutics, Inc., Biovest International, Inc., ImmunoCellular Therapeutics, Ltd., Immune Design, Inc., Inovio Pharmaceuticals, Inc., Intrexon Corporation and Northwest Biotherapeutics, Inc. Even if we obtain regulatory approval of our product candidates, the availability and price of our competitors' products could limit the demand and the price we are able to charge for our product candidates. We may not be able to implement our business plan if the acceptance of our product candidates is inhibited by price competition or the reluctance of physicians to switch from existing methods of treatment to our product candidates, or if physicians switch to other new drug or biologic products or choose to reserve our product candidates for use in limited circumstances. For additional information regarding our competition, see "Item 1. Business—Competition."

We are highly dependent on our key personnel, and if we are not successful in attracting and retaining highly qualified personnel, we may not be able to successfully implement our business strategy.

Our ability to compete in the highly competitive biotechnology and pharmaceutical industries depends upon our ability to attract and retain highly qualified managerial, scientific and medical personnel. We are highly dependent on our management, scientific and medical personnel, including our Chief Executive Officer, our Chief Financial Officer, our Chief Operating Officer, our Chief Medical Officer and Chief Technology Officer, and our Chief Scientific Officer. The loss of the services of any of our executive officers, other key employees, and other scientific and medical advisors, and our inability to find suitable replacements could result in delays in product development and harm our business.

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

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

As of December 31, 2014, we had 35 employees, all of whom were full-time. As our development and commercialization plans and strategies develop, and as we transition into operating as a public company, we expect to need additional managerial, operational, sales, marketing, financial and other personnel. Future growth would impose significant added responsibilities on members of management, including:

- identifying, recruiting, integrating, maintaining and motivating additional employees;

- managing our internal development efforts effectively, including the clinical and FDA review process for our product candidates, while complying with our contractual obligations to contractors and other third parties; and
- improving our operational, financial and management controls, reporting systems and procedures.

There are a small number of individuals with experience in cell therapy and the competition for such individuals is high. Our future financial performance and our ability to commercialize our product candidates will depend, in part, on our ability to effectively manage any future growth, and our management may also have to divert a disproportionate amount of its attention away from day-to-day activities in order to devote a substantial amount of time to managing these growth activities. We currently rely, and for the foreseeable future will continue to rely, in substantial part on certain independent organizations, advisors and consultants to provide certain services, including substantially all aspects of regulatory approval, clinical management, and manufacturing. There can be no assurance that the services of independent organizations, advisors and consultants will continue to be available to us on a timely basis when needed, or that we can find qualified replacements. In addition, if we are unable to effectively manage our outsourced activities

or if the quality or accuracy of the services provided by consultants is compromised for any reason, our clinical trials may be extended, delayed or terminated, and we may not be able to obtain regulatory approval of our product candidates or otherwise advance our business. There can be no assurance that we will be able to manage our existing consultants or find other competent outside contractors and consultants on economically reasonable terms, or at all.

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

In addition to expanding our organization, we expect to increase the size of our facility and build out our development and manufacturing capabilities, which will require significant capital expenditures. If these capital expenditures are higher than expected, it may adversely affect our financial condition and capital resources. In addition, if the increase in the size of our facility is delayed, it may limit our ability to rapidly expand the size of our organization in order to meet our corporate goals.

If we fail to obtain additional financing, we may be unable to complete the development and commercialization of our product candidates.

Our operations have consumed substantial amounts of cash since inception. We expect to continue to spend substantial amounts to continue the clinical development of our product candidates, including our planned clinical development and preclinical studies of our product candidates and other programs. If approved, we will require significant additional amounts in order to launch and commercialize our product candidates.

As of December 31, 2014, we had cash and cash equivalents of approximately \$191.6 million, which included the net proceeds from our recently completed initial public offering. We believe that such cash and cash equivalents will be sufficient to fund our operations through at least the first half of 2017. However, changing circumstances may cause us to consume capital significantly faster than we currently anticipate, and we may need to spend more money than currently expected because of circumstances beyond our control. We may require additional capital for the further development and commercialization of our product candidates and may need to raise additional funds sooner if we choose to expand more rapidly than we presently anticipate.

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

Any of the above events could significantly harm our business, prospects, financial condition and results of operations and cause the price of our common stock to decline.

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

We may seek additional capital through a combination of public and private equity offerings, debt financings, strategic partnerships and alliances and licensing arrangements. To the extent that we raise additional capital through the sale of equity or convertible debt securities, the ownership interests of our existing stockholders will be diluted, and the terms may include liquidation or other preferences that adversely affect the rights of our stockholders. The incurrence of indebtedness would result in increased fixed payment obligations and could involve certain restrictive



covenants, such as limitations on our ability to incur additional debt, limitations on our ability to acquire or license intellectual property rights and other operating restrictions that could adversely impact our ability to conduct our business. If we raise additional funds through strategic partnerships and alliances and licensing arrangements with third parties, we may have to relinquish valuable rights to our technologies or product candidates, or grant licenses on terms unfavorable to us.

We need to oversee manufacturing of a complex supply chain of cellular therapy product candidates, viral vectors and small molecule drugs.

Because of the complex nature of our products, we need to oversee manufacture of multiple components that require a diverse knowledge base and appropriate manufacturing personnel. The supply chain for these components is separate and distinct, and no single manufacturer can supply more than one component of each of our products. Additionally, it is likely that the cell therapy products will need to be made within an appropriate geographic location for the area in which the products will be utilized, so one cell

therapy manufacturing facility may not be able to supply diverse geographic areas. Any lack of capabilities to store, freeze, thaw and infuse our cell therapies would adversely affect our business and prospects.

We expect to rely on third parties to manufacture a substantial portion of our clinical cell therapy product candidates, viral vectors and small molecule supplies in the United States and Europe.

We do not currently own any facility that may be used as our clinical-scale manufacturing and processing facility, and must currently rely on outside vendors to manufacture supplies and process our product candidates, which is and will need to be done on a patient-by-patient basis. We have not yet caused our product candidates to be manufactured or processed on a commercial scale. We may not be able to scale patient-by-patient manufacturing and processing to satisfy clinical or commercial demands for any of our product candidates. In addition, our anticipated reliance on a limited number of third-party manufacturers exposes us to the following risks:

- We may be unable to identify manufacturers on acceptable terms or at all because the number of potential manufacturers is limited and the FDA or an equivalent foreign regulatory agency must approve any replacement contractor. This approval would require new testing and compliance inspections. In addition, a new manufacturer would have to be educated in, or develop substantially equivalent processes for, production of our products after receipt of FDA approval, if any.
- Our third-party manufacturers might be unable to timely formulate and manufacture our product or produce the quantity and quality required to meet our clinical and commercial needs, if any.
- Contract manufacturers may not be able to execute our manufacturing procedures appropriately.
- Our future contract manufacturers may not perform as agreed or may not remain in the contract manufacturing business for the time required to supply our clinical trials or to successfully produce, store and distribute our products.
- Manufacturers are subject to ongoing periodic unannounced inspection by the FDA, the Drug Enforcement Administration, or corresponding agencies in other geographic locations, to ensure strict compliance with cGMP and other government regulations and corresponding foreign standards. We do not have control over third-party manufacturers' compliance with these regulations and standards.
- We may not own, or may have to share, the intellectual property rights to any improvements made by our third-party manufacturers in the manufacturing process for our products.
- Our third-party manufacturers could breach or terminate their agreement with us.

Each of these risks could delay our clinical trials, the approval, if any of our product candidates by the FDA or the commercialization of our product candidates or result in higher costs or deprive us of potential product revenue. In addition, we will rely on third parties to perform release tests on our product candidates prior to delivery to patients. If these tests are not appropriately done and test data are not reliable, patients could be put at risk of serious harm.

We expect to create our own manufacturing facility for supply of U.S. clinical and/or commercial cell therapy product candidate requirements, but there is no guarantee we will be able to do so.

Our intent to create internal manufacturing infrastructure will rely upon finding personnel with an appropriate background and training to staff and operate the facility on a daily basis. Should we be unable to find such individuals, we may need to rely on external contractors longer than anticipated, and train additional personnel to fill the needed roles. There are a small number of individuals with experience in cell therapy and the competition for such individuals is high.

Specifically, the establishment of a cell-therapy manufacturing facility is a complex endeavor requiring knowledgeable individuals who have successful previous experience in cleanroom designs. Cell therapy facilities, like other biological agent manufacturing facilities, require appropriate commissioning and validation activities to demonstrate that they operate as designed. Additionally, each manufacturing process must be validated through the performance of process validation runs to guarantee that the facility, personnel, equipment, and process work as designed. While we have developed our own manufacturing processes using an in-house process development team to

maximize our understanding of our process, there is timing risk associated with in-house product manufacture.

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

Gene-modified cell therapy manufacture requires many specialty raw materials, some of which are manufactured by small companies with limited resources and experience to support a commercial product. Some suppliers typically support biomedical researchers or blood-based hospital businesses and may not have the capacity to support commercial products manufactured under cGMP by biopharmaceutical firms. The suppliers may be ill-equipped to support our needs, especially in non-routine circumstances like an FDA

inspection or medical crisis, such as widespread contamination. We also do not have commercial supply arrangements with many of these suppliers, and may not be able to contract with them on acceptable terms or at all. Accordingly, we may experience delays in receiving key raw materials to support clinical or commercial manufacturing.

In addition, 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.

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

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

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

We may not be able to develop in-house sales and distribution capabilities or establish or maintain relationships with third-party collaborators to commercialize any product in the United States or overseas.

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

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

- differing regulatory requirements in foreign countries;
- unexpected changes in tariffs, trade barriers, price and exchange controls and other regulatory requirements;
- economic weakness, including inflation, or political instability in particular foreign economies and markets;
- compliance with tax, employment, immigration and labor laws for employees living or traveling abroad;
- foreign taxes, including withholding of payroll taxes;
- foreign currency fluctuations, which could result in increased operating expenses and reduced revenue, and other obligations incident to doing business in another country;
- difficulties staffing and managing foreign operations;
- workforce uncertainty in countries where labor unrest is more common than in the United States;
- potential liability under the Foreign Corrupt Practices Act of 1977 or comparable foreign regulations;
- challenges enforcing our contractual and intellectual property rights, especially in those foreign countries that do not respect and protect intellectual property rights to the same extent as the United States;
- production shortages resulting from any events affecting raw material supply or manufacturing capabilities abroad;
- and
- business interruptions resulting from geo-political actions, including war and terrorism.

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

We may form or seek strategic alliances or enter into additional licensing arrangements in the future, and we may not realize the benefits of such alliances or licensing arrangements.

We may form or seek strategic alliances, create joint ventures or collaborations or enter into additional licensing arrangements with third parties that we believe will complement or augment our development and commercialization efforts with respect to our product candidates and any future product candidates that we may develop. Any of these relationships may require us to incur non-recurring and other charges, increase our near and long-term expenditures, issue securities that dilute our existing stockholders or disrupt our management and business. In addition, we face significant competition in seeking appropriate strategic partners and the negotiation process is time-consuming and complex. Moreover, we may not be successful in our efforts to establish a strategic partnership or other alternative arrangements for our product candidates because they may be deemed to be at too early of a stage of development for collaborative effort and third parties may not view our product candidates as having the requisite potential to demonstrate safety and efficacy. If we license products or businesses, we may not be able to realize the benefit of such transactions if we are unable to successfully integrate them with our existing operations and company culture. We cannot be certain that, following a strategic transaction or license, we will achieve the revenue or specific net income that justifies such transaction. Any delays in entering into new strategic partnership agreements related to our product candidates could delay the development and commercialization of our product candidates in certain geographies for certain indications, which would harm our business prospects, financial condition and results of operations.

Our reliance on third parties requires us to share our trade secrets, which increases the possibility that a competitor will discover them or that our trade secrets will be misappropriated or disclosed.

Because we rely on third parties to manufacture our drug substance and our drug product, and because we collaborate with various organizations and academic institutions on the advancement of our technology platform, we must, at times, share trade secrets with them. We seek to protect our proprietary technology in part by entering into confidentiality agreements and, if applicable, material transfer agreements, collaborative research agreements, consulting agreements or other similar agreements with our collaborators, advisors, employees and consultants prior to beginning research or disclosing proprietary information. These agreements typically limit the rights of the third parties to use or disclose our confidential information, such as trade secrets. Despite these contractual provisions, the need to share trade secrets and other confidential information 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. Given that our proprietary position is based, in part, on our know-how and trade secrets, a competitor's discovery of our trade secrets or other unauthorized use or disclosure would impair our competitive position and may have a material adverse effect on our business.

We may use our financial and human resources to pursue a particular research program or product candidate and fail to capitalize on programs or product candidates that may be more profitable or for which there is a greater likelihood of success.

Because we have limited resources, we may forego or delay pursuit of opportunities with certain programs or product candidates or for indications that later prove to have greater commercial potential. Our resource allocation decisions may cause us to fail to capitalize on viable commercial products or profitable market opportunities. Our spending on current and future research and development programs for product candidates may not yield any commercially viable products. If we do not accurately evaluate the commercial potential or target market for a particular product candidate, we may relinquish valuable rights to that product candidate through strategic collaboration, licensing or other royalty arrangements in cases in which it would have been more advantageous for us to retain sole development and commercialization rights to such product candidate, or we may allocate internal resources to a product candidate in a therapeutic area in which it would have been more advantageous to enter into a partnering arrangement. We are particularly susceptible to this risk because we are pursuing clinical and preclinical development program in each of our CaspaCIDE, DeCIDE, CIDE CAR and GoCAR-T technologies. Resources spent on one of these programs could result in fewer resources to further develop the other programs.

We have limited information available regarding the ultimate cost of our products, and cannot estimate what the cost of our products will be upon commercialization, should that occur.

We do not yet have sufficient information to reliably estimate the cost of the commercial manufacturing and processing of our product candidates, and the actual cost to manufacture and process our product candidates could materially and adversely affect the commercial viability of our product candidates. As a result, we may never be able to develop a commercially viable product. Because of the patient-specific nature of our manufacturing process, it is not amenable to traditional “scale up” to manufacture larger lots as is performed for traditional drugs and biological agents.

We and our contractors utilize hazardous materials in our business operations, and any claims relating to improper handling, storage, or disposal of these materials could harm our business.

Our activities involve the controlled use of potentially hazardous substances, including chemical and biological materials, by our third-party manufacturers. Our manufacturers are subject to federal, state and local laws and regulations in the United States governing the use, manufacture, storage, handling and disposal of medical and hazardous materials, and similar laws in other geographic regions. Although we believe that our manufacturers' procedures for using, handling, storing and disposing of these materials comply with legally prescribed standards, we cannot completely eliminate the risk of contamination or injury resulting from medical or hazardous materials. As a result of any such contamination or injury, we may incur liability or local, city, state or federal authorities may curtail the use of these materials and interrupt our business operations. In the event of an accident, we could be held liable for damages or penalized with fines, and the liability could exceed our resources. We do not have any insurance for liabilities arising from medical or hazardous materials. Compliance with applicable environmental laws and regulations is expensive, and current or future environmental regulations may impair our research, development and production efforts, which could harm our business, prospects, financial condition or results of operations.

Our internal computer systems, or those used by our clinical investigators, contractors or consultants, may fail or suffer security breaches.

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

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

Our operations, and those of our clinical investigators, contractors and consultants, could be subject to power shortages, telecommunications failures, water shortages, floods, earthquakes, hurricanes, typhoons, fires, extreme weather conditions, medical epidemics and other natural or man-made disasters or business interruptions, for which we are predominantly self-insured. The occurrence of any of these business disruptions could seriously harm