BELLICUM PHARMACEUTICALS, INC
Form 10-K
March 13, 2017

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UNITED STATES
SECURITIES AND EXCHANGE COMMISSION
Washington, D.C. 20549
Form 10-K
(Mark One)
x ANNUAL REPORT PURSUANT TO SECTION 13 OR 15(d) OF THE SECURITIES EXCHANGE ACT OF 1934
For the fiscal year ended December 31, 2016
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)
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 x
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 x
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 x 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 x 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. x

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 x |
| 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 x

The approximate aggregate market value of the voting and non-voting common equity held by non-affiliates of the Registrant, based upon the last sale price of the common stock reported on The NASDAQ Global Market as of June 30, 2016 was $251,404,832. *

As of February 28, 2017, there were 27,157,680 shares of the Registrant's common stock, par value $0.01 per share, outstanding.

DOCUMENTS INCORPORATED BY REFERENCE

Portions of the Registrant’s definitive Proxy Statement relating to its 2017 Annual Meeting of Stockholders are incorporated by reference into Part III of this Annual Report on Form 10-K. Such Proxy Statement will be filed with the U.S. Securities and Exchange Commission within 120 days following the Registrant’s fiscal year ended December 31, 2016.

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*Excludes 7,644,2070 shares of common stock held by directors and officers and by stockholders that the registrant concluded were affiliates of the Registrant as of June 30, 2016. Exclusion of such shares should not be construed to indicate that any such holder possesses the power, direct or indirect, to direct or cause the direction of the management or policies of the Registrant, or that such person is controlled by or under common control with the Registrant.

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## SPECIAL NOTE REGARDING 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,” “pot “predict,” “project,” “should,” “will,” “would” or the negative of those terms, and similar expressions that convey uncertainty o 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 Chemical Induction of Dimerization, or CID, CID-based technologies, including CaspaCIDe and GoCAR-T;
- 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 and the success of any such collaborations;
- 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, or U.S., 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 cash and other resources; and
- our expectations regarding our ability to obtain and maintain intellectual property protection for our product candidates.

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.

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.

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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. We are using our proprietary CID technology platform to engineer our product candidates with switch technologies that are designed to 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, chimeric antigen receptor T cell therapy, or CAR T, and T cell receptors, or TCRs. HSCT, also known as bone marrow transplantation, has for decades been curative for many patients with hematological cancers or orphan inherited blood disorders. However, adoption of HSCT to date has been limited by the risks of transplant-related morbidity and mortality from graft-versus-host-disease, or GvHD, and the potential for serious infections due to the lack of an effective immune system following a transplant. CAR T and TCR cell therapies are an innovative approach in which a patient's T cells are genetically modified to carry chimeric antigen receptors, or CARs, or TCRs 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," or CRS, neurologic toxicities and cases in which they have attacked healthy organs. In each case, these toxicities have sometimes resulted in 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 that raise even greater safety concerns.

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, 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 and/or persistence of the immunotherapy cells. Each of our product candidates incorporates one of these switches, for enhanced, real time control of safety and efficacy:

- CaspaCIDe is our safety switch, incorporated into our HSCT and TCR product candidate, where it is inactive unless the patient experiences a serious side effect. In that event, rimiducid is administered to induce Caspase-9, or iCaspase, switch activation to fully or partially eliminate the cells, with the goal of terminating or attenuating the therapy and resolving the serious side effect.

- Our "Go" switch incorporated into our GoCAR-T product candidates, is an activation switch designed to allow control of the activation and proliferation of the 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, reducing the dosage per infusion, or suspending further rimiducid administration.

In addition, we have an active research effort to develop other advanced molecular switch approaches, including a "dual-switch" that is designed to provide a user-controlled system for managing persistence and safety of tumor antigen-specific CAR T cells.

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 lead clinical product candidate is described below.

- BPX-501 is a CaspaCIDe product candidate designed as an adjunct T cell therapy administered after allogeneic HSCT. BPX-501 is designed to improve transplant outcomes by enhancing the recovery of the immune system following an HSCT procedure. BPX-501 addresses the risk of infusing donor T cells by enabling the elimination of donor T cells through the activation of the CaspaCIDe safety switch if there is an emergence of uncontrolled GvHD.

The European Commission has granted orphan drug designations to BPX-501 for treatment in HSCT, and for activator agent rimiducid for the treatment of GvHD. Additionally, BPX-501 and rimiducid have received orphan drug status from the U.S. Food and

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Drug Administration, or the FDA, as a combination replacement T-cell therapy for the treatment of immunodeficiency and GvHD after allogeneic HSCT.

During 2016, we discussed with the European Medicines Agency, or the EMA, clinical and regulatory plans to support the filing of Marketing Authorization Applications, or MAAs, for BPX-501 and rimiducid in Europe, initially for pediatric patients with certain orphan inherited blood disorders or treatment-refractory hematological cancers. Based on the regulatory discussions, we believe that data from the European arm of our BP-004 trial, expanded to enroll additional patients, with a primary endpoint of event-free survival (death, severe GvHD and severe infection) at six months, could form the basis of MAAs for BPX-501 and rimiducid. In addition, the EMA's Committee for Medicinal Products for Human Use, or the CHMP, has agreed that review and approval under "exceptional circumstances" may be suitable, recognizing that a randomized trial may not be feasible in the pediatric haploidentical hematopoeitic stem cell transplant setting. Exceptional circumstances may be granted for medicines that treat very rare diseases, or where controlled studies are impractical or not consistent with accepted principles of medical ethics. In place of a randomized trial, we intend to collect data from a concurrent observational study in the pediatric matched unrelated donor hematopoietic stem cell transplant setting, which will include both retrospective patients and prospective patients.

We have discussions ongoing with the FDA regarding the regulatory path to approval in the U.S. and we expect to provide updates in the first half of 2017.

In addition to BPX-501, our clinical stage product candidates which are designed to overcome limitations of CAR T and TCR therapies, include the following:

- BPX-701 is a CaspaCIDe-enabled natural high affinity TCR product candidate designed to target malignant cells expressing the preferentially-expressed antigen in melanoma, or PRAME. Initial planned indications for BPX-701 development are refractory or relapsed acute myeloid leukemia, or AML, and myelodysplastic syndromes, or MDS, with an additional study planned for metastatic uveal melanoma. Each of these is an orphan indication where PRAME is highly expressed and for which current treatment options are limited. A Phase 1 dose finding clinical trial in patients with relapsed or refractory myeloid neoplasms is being conducted at the Oregon Health & Science University Hospital in Portland, Oregon.

- BPX-601 is a GoCAR-T product candidate containing our proprietary inducible MyD88/CD40, or iMC, activation switch, designed to treat solid tumors expressing prostate stem cell antigen, or PSCA. Preclinical data shows enhanced T cell proliferation, persistence and in vivo anti-tumor activity compared to traditional CAR T therapies. A Phase 1 clinical trial in patients with non-resectable pancreatic cancer is being conducted at the Baylor Sammons Cancer Center in Dallas, Texas.

We have developed an efficient and scalable process to manufacture genetically modified T cells of high quality, which is currently being used by our third-party contract manufacturers to produce BPX-501 for our clinical trials. We are leveraging this process, as well as our resources, capabilities and expertise for the manufacture of our CAR T and TCR product candidates.

Pipeline

The following table summarizes our product candidate pipeline:

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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.

The following therapeutic applications of cellular immunotherapy have been 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 chronic myeloid leukemia. 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.

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:

| Cellular Immunotherapy Approach | Safety Challenges | Efficacy Challenges |
|---|---|---|
| Allogeneic HSCT | GvHD and viral infections are frequent and potentially fatal side effects | Attempts to control GvHD (steroids, T Cell depletion, etc.) increase likelihood of non-engraftment, relapse of underlying disease and viral infection |
| CAR T | Serious immune toxicity (CRS) or neurotoxicity | CARs have not demonstrated the same high response rates to solid tumor antigens as have been seen against CD19-positive homological malignancies |
| | Standard-of-care (steroids) and/or cytokine receptor antagonists, such as tocilizumab, can be ineffective; long ICU stay, relapse of underlying disease, infections and death | Small number of validated tumor-specific antigens that can be targeted |
| | Other safety approaches* have slow onset of action or have safety issues of their own | For certain antigen targets, severe toxicity from treatment prevents sufficient therapeutic window for clinical benefit |
| TCR | High risk of off-target or off-organ toxicities | Human clinical data still early |

* See discussion of other approaches below under "Our Proprietary Switch Technologies - CaspaCIDe"

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

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infusion of a small molecule, rimiducid, instead of by natural upstream signals. Our current 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 apoptosis, and the "activation switch" is designed to lead to proliferation and/or activation and/or persistence 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 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-9i: Signaling Molecule for Apoptosis. Caspase-9, or iCaspase is the initiating enzyme in the apoptosis pathway. When activated, caspase starts a signaling cascade, including the activation of caspase-3, which ultimately leads to apoptosis, a non-inflammatory process of cell elimination.
- iMC: 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.

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 two most advanced switch technologies.

| | CaspaCIDe | GoCAR-T |
|---|---|---|
| Cell Type | Donor T cells (HSCT) or patient T cells (TCRs) | Patient T cells |
| Proprietary Components | iCaspase - safety switch | iMC co-stimulation switch |
| Applications | HSCT and TCR therapy | CAR T therapy |
| Potential Safety Benefit | Modulation of effect with rimiducid triggers T cell apoptosis | Modulation of effect with rimiducid triggers T-cell activation & proliferation |