

Calithera Biosciences, Inc.
Form 10-K
March 16, 2017

UNITED STATES

SECURITIES AND EXCHANGE COMMISSION

Washington, D.C. 20549

FORM 10-K

(Mark One)

ANNUAL REPORT PURSUANT TO SECTION 13 OR 15(d) OF THE SECURITIES EXCHANGE ACT OF 1934
For the fiscal year ended December 31, 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 001-36644

CALITHERA BIOSCIENCES, INC.

(Exact name of Registrant as specified in its Charter)

Delaware (State or other jurisdiction of incorporation or organization)	27-2366329 (I.R.S. Employer Identification No.)
343 Oyster Point Blvd., Suite 200 South San Francisco, CA (Address of principal executive offices)	94080 (Zip Code)

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Registrant's telephone number, including area code: (650) 870-1000

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

Common Stock, Par Value \$0.0001 Per Share (Title of each class)	The NASDAQ Global Select Market (Name of each exchange on which registered)
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Securities registered pursuant to section 12(g) of the Act: None

Indicate by check mark if the Registrant is a well-known seasoned issuer, as defined in Rule 405 of the Securities Act. YES NO

Indicate by check mark if the Registrant is not required to file reports pursuant to Section 13 or 15(d) of the Act. YES NO

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

Indicate by check mark whether the Registrant has submitted electronically and posted on its corporate Web site, if any, every Interactive Data File required to be submitted and posted pursuant to Rule 405 of Regulation S-T (§232.405 of this chapter) during the preceding 12 months (or for such shorter period that the Registrant was required to submit and post such files). YES NO

Indicate by check mark if disclosure of delinquent filers pursuant to Item 405 of Regulation S-K (§229.405) 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 Annual Report on Form 10-K or any amendment to this Annual Report on 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 definition of "large accelerated filer", "accelerated filer", and "smaller reporting company" in Rule 12b-2 of the Exchange Act. (Check one):

Large accelerated filer	Accelerated filer
Non-accelerated filer (Do not check if a small reporting company)	Small reporting company

Indicate by check mark whether the Registrant is a shell company (as defined in Rule 12b-2 of the Exchange Act). YES NO

The aggregate market value of the registrant's common stock held by non-affiliates of the registrant as of the last business day of the registrant's most recently completed second fiscal quarter was approximately \$52.3 million, based on the closing price of the registrant's common stock on the NASDAQ Global Select Market of \$3.71 per share.

The number of shares of Registrant's Common Stock outstanding as of March 10, 2017 was 27,425,081.

DOCUMENTS INCORPORATED BY REFERENCE

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Portions of the Registrant's Definitive Proxy Statement relating to the 2016 Annual Meeting of Stockholders will be filed with the Securities and Exchange Commission within 120 days after the end of the fiscal year covered by this Annual Report on Form 10-K and are incorporated by reference into Part III of this Annual Report on Form 10-K.

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CAUTIONARY INFORMATION REGARDING FORWARD-LOOKING STATEMENTS

This Annual Report on Form 10-K for the year ended December 31, 2016, contains forward-looking statements within the meaning of Section 27A of the Securities Act of 1933, as amended, or the Securities Act, and Section 21E of the Securities Exchange Act of 1934, as amended, or the Exchange Act, which are subject to the “safe harbor” created by those sections, concerning our business, operations, and financial performance and condition as well as our plans, objectives, and expectations for business operations and financial performance and condition. Any statements contained herein that are not of historical facts may be deemed to be forward-looking statements. You can identify these statements by words such as “anticipate,” “assume,” “believe,” “could,” “estimate,” “expect,” “intend,” “may,” “plan,” “would,” and other similar expressions that are predictions of or indicate future events and future trends. These forward-looking statements are based on current expectations, estimates, forecasts, and projections about our business and the industry in which we operate and management's beliefs and assumptions and are not guarantees of future performance or development and involve known and unknown risks, uncertainties, and other factors that are in some cases beyond our control. As a result, any or all of our forward-looking statements in this Annual Report on Form 10-K may turn out to be inaccurate. Factors that could materially affect our business operations and financial performance and condition include, but are not limited to, those risks and uncertainties described herein under “Item 1A - Risk Factors.” You are urged to consider these factors carefully in evaluating the forward-looking statements and are cautioned not to place undue reliance on the forward-looking statements. The forward-looking statements are based on information available to us as of the filing date of this Annual Report on Form 10-K. Unless required by law, we do not intend to publicly update or revise any forward-looking statements to reflect new information or future events or otherwise. You should, however, review the factors and risks we describe in the reports we will file from time to time with the Securities and Exchange Commission, or the SEC, after the date of this Annual Report on Form 10-K.

PART I

Item 1. Business.

Overview

We are a clinical-stage pharmaceutical company focused on discovering and developing novel small molecule oncology drugs directed against tumor and immune cell targets that control key metabolic pathways in the tumor microenvironment. Tumor metabolism and immuno-oncology have emerged as promising new fields for cancer drug discovery, and recent clinical successes with therapeutic agents in each field have demonstrated the potential to create fundamentally new therapies for cancer patients. We are developing agents that take advantage of the unique metabolic requirements of tumor cells and cancer-fighting immune cells such as cytotoxic T-cells. Our lead product candidate, CB-839, is an internally discovered, first-in-class oral inhibitor of glutaminase, a critical enzyme in tumor cells. We are currently evaluating CB 839 in multiple Phase 1b/2 clinical trials in solid tumors. CB-839 administered as a single agent has resulted in clinical responses in renal cell cancer and acute myeloid leukemia and clinical benefit in several other tumor types. We are currently enrolling patients in a series of combination Phase 1b cohorts in specific solid tumor types, and are planning to begin Phase 2 trials in renal cell carcinoma and triple negative breast cancer in 2017. Our second product candidate, CB 1158, is a first-in-class oral inhibitor of arginase, an enzyme that depletes the amino acid arginine, a key metabolic nutrient for T cells, and is being co-developed with Incyte Pharmaceuticals for hematology and oncology indications. CB-1158 is currently being tested alone and will be tested in combination with a checkpoint inhibitor in a Phase 1/2 clinical trial in patients with solid tumors. We also have ongoing research efforts that are focused on discovering additional product candidates against novel tumor metabolism and immunology targets.

Our lead product candidate, CB-839, takes advantage of the pronounced dependency many cancers have on the nutrient glutamine for growth and survival. CB-839 inhibits glutaminase, an enzyme required by cancer cells to utilize glutamine effectively. In preclinical studies, CB-839 demonstrated broad antitumor activity in tumor cell lines, inhibited the growth of human tumors in animal models and was well tolerated in toxicity studies. CB-839 was also synergistic with several approved, standard of care, cancer therapeutics. We believe CB-839 has the potential to be an important new therapeutic agent with a novel mechanism of action for the treatment of a broad range of cancers, and is the only selective glutaminase inhibitor currently in clinical trials. We currently retain all commercial rights to CB-839 and have been granted a U.S. patent, which includes composition of matter coverage for CB-839 through 2032.

CB-839 may also have the potential to work in combination with immuno-oncology (I-O) therapeutics. Inhibition of glutaminase results in accumulation of glutamine, the substrate of glutaminase, in tumors. Glutamine, which is frequently depleted in the tumor microenvironment due to avid uptake by tumor cells, has been shown to be an important nutrient for T-cell proliferation. Administration of CB-839 to tumor-bearing animals substantially enhances the anti-tumor activity of checkpoint inhibitors, potentially by restoring the levels of glutamine in the tumor microenvironment and thereby enabling T-cells to proliferate. Checkpoint inhibitors,

including the approved agents nivolumab (marketed as Opdivo) and pembrolizumab (marketed as Keytruda), are a class of immuno-oncology agents directed against programmed death protein-1 (PD-1) or programmed death ligand-1 (PD-L1) that promote the activation and tumor-killing properties of the patient's own immune cells, such as cytotoxic T-cells. CB-839 could potentially have multiple mechanisms of action in the treatment of cancer first by starving the tumor cell, and second by facilitating the activation of T-cells in the nutrient-deprived tumor microenvironment.

Our second product candidate, CB-1158, is a potent and selective orally bioavailable inhibitor of the enzyme arginase, that was discovered at Calithera and is being co-developed with Incyte Corporation. Arginase depletes arginine, a nutrient that is critical for the activation and proliferation of the body's cancer-fighting immune cells, such as cytotoxic T-cells and natural killer (NK)-cells. During normal activation of the immune system, arginase, which is expressed by suppressive myeloid immune cells, plays an important role in halting T-cell proliferation. But in many tumors, including lung, gastrointestinal, bladder, renal cancer and acute myeloid leukemia, arginase-expressing myeloid cells accumulate and maintain an immunosuppressive environment, blocking the ability of T-cells and NK-cells to kill cancer cells. We believe that inhibitors of arginase can promote an anti-tumor immune response by restoring arginine levels, thereby allowing activation of the body's own immune cells, including cytotoxic T-cells and NK-cells.

Our Research and Development Programs

The following table summarizes our ongoing and planned clinical trials for our lead programs in tumor metabolism and tumor immunology. We also intend to develop additional product candidates from our research and discovery efforts in these fields.

The Evolution of Cancer Therapeutic Agents

Cancer is characterized by the uncontrolled growth of aberrant cells in the body, leading to the invasion of essential organs and often death. Unlike normal cells, which grow only in response to carefully regulated signals from the body, cancer cells are able to proliferate largely without external signals. Cancer cells have gained this ability as the result of genetic alterations that change protein expression or function. Invasive tumors, also known as metastatic tumors, which are the greatest threat to patients, typically have multiple mutations, deletions or amplifications of genes encoding key proteins that regulate cell growth. These alterations allow the cancer cell to grow, invade other tissues, and avoid recognition and destruction by the body's immune system.

Initially, the pharmacological treatment of cancer utilized non-specific cytotoxic agents that targeted all rapidly dividing cells, including normal cells. These non-specific cytotoxic agents have anti-tumor effects but their use is often limited by severe toxicities. As the understanding of the proteins and pathways that enable cancer cells to thrive has evolved, newer more targeted agents have been developed that block specific proteins that are activated in cancer cells.

Tumor metabolism and tumor immunology represent two emerging fields for the development of therapeutics that can address the challenges presented in treating cancers with multiple mutations or with mutations that are difficult to inhibit. Certain fundamental changes in the metabolic pathways of cancer cells are observed in many cancer types with different mutational

backgrounds. Therapeutic agents that can take advantage of these changes in metabolism have the potential to act broadly against many cancers. Similarly, genetically diverse tumor types have developed mechanisms to escape destruction by the body's immune system. Pharmacological activation of the immune system with agents such as ipilimumab (marketed as Yervoy) and nivolumab (marketed as Opdivo), has resulted in favorable outcomes in melanoma, non-small cell lung cancer and renal cell cancer. We believe additional opportunities exist to develop novel therapeutics that can further enhance the cancer-fighting ability of the immune system, either as single agents, or in combination with approved therapeutics.

Rationale for Targeting Tumor Cell Metabolism

Cancer cells acquire the ability to grow rapidly and spread to new sites in the body by accumulating genetic alterations in important genes that control growth and survival. These same genetic changes also result in altered metabolic pathways within the cancer cells that fuel the high demand for energy and the production of new proteins, lipids, RNA and DNA needed for rapid proliferation. We and others have observed that many types of cancer cells develop a unique dependence on specific metabolic pathways upon which normal cells are not reliant. Accordingly, when these metabolic pathways are blocked, cancer cells are essentially starved of critical nutrients and stop growing or die, whereas normal cells are largely unaffected.

Alterations in the fundamental metabolic pathways of tumors often cause a dramatic rise in the uptake of the nutrients glucose and glutamine. Uptake of these agents is often significantly greater in tumor tissue than in surrounding normal tissue. We believe this enhanced uptake of glucose and glutamine by tumors occurs because of their greater need for these nutrients for growth and survival. The primary goal of drugs targeting tumor metabolism pathways is to take advantage of cancer-specific nutrient dependencies to block cancer growth. Changes in cellular metabolism are remarkably consistent across many tumor types, yet fundamentally different from normal cells, providing the potential to develop broadly applicable agents that target these altered pathways, but have less toxicity than standard cytotoxic agents.

Rationale for Targeting Immune Cell Metabolism

The immune system has evolved in higher organisms to recognize self from non-self. Immune surveillance is the process whereby the body identifies pathogens as well the abnormal cells that are infected with viruses or have become cancerous. The immune system has a number of mechanisms that recognize differences between cell surface components on abnormal cells that are new or are modified from those of normal cells. Upon recognition of "foreign" cells, a number of processes are activated to allow the direct attack and clearance of abnormal cells. However, excessive or inappropriate activation of the immune system can have negative consequences such as autoimmune disease, inflammation, and rejection of a fetus. Compensatory inhibitory mechanisms have evolved to control excessive inflammatory activity by dampening the immune stimulation. These immunostimulatory and immunoinhibitory mechanisms provide a constant balance that is thought to result, under most circumstances, in the identification and clearance of infected or cancerous cells without excessive stimulation. Mutated cells that successfully evade immune surveillance do so, in part, by blocking or reducing immunostimulatory and/or enhancing immunoinhibitory activities. Immuno-oncology therapies are in development that interfere with mechanisms that tumors have used to evade immune surveillance. Immune checkpoint proteins including PD-1, PD-L1 and CTLA-4 are specific molecules on tumor cells and T-cells that reduce the ability of T-cells to accomplish cytotoxic killing of tumor cells. Antibodies to PD-1, PD-L1 and CTLA-4, known as checkpoint inhibitors, block these molecules and allow T cells to become activated and to kill tumor cells. These agents have allowed substantial, long-term benefit to a subset of patients.

Activated T-cells have specific nutritional requirements that are often not available within the tumor microenvironment including, in specific tumors, tryptophan, glutamine, and arginine, as shown in the diagram

below. Each of these nutrients is depleted within the microenvironment by a different mechanism. Tryptophan is depleted by the action of indolamine dioxygenase, or IDO, an enzyme found in dendritic cells, certain other immune cells, and occasionally in tumors themselves. Glutamine depletion results from the avid uptake of this amino acid by tumor cells that have a very high requirement of this nutrient for growth and survival. Arginine is cleared directly from the tumor environment by arginase secreted from myeloid-derived suppressor cells, or MDSCs, and neutrophils. The end result of each of these mechanisms has been shown to be loss of T-cell or NK-cell activation and/or proliferation, resulting in the blunting of the immune response to tumor cells.

Calithera is developing agents that are aimed at supporting the nutritional needs of T-cells and NK cells for glutamine and arginine, allowing the proliferation and activation of quiescent T-cells. This program is analogous to the effect of IDO on the availability of tryptophan in the tumor microenvironment. We are evaluating both CB-839 and CB-1158 in combination with immune therapies during clinical development.

Our Programs

Our Glutaminase Program—a Dual Tumor Metabolism and Immuno-Oncology Target

It has been understood for more than 50 years that most cancer cells require glutamine to thrive. Removal of glutamine leads to a substantial reduction in cell growth or induces cell death in glutamine-dependent cancer cells. Normal cells do not show this pronounced dependence on glutamine. This contrast has prompted significant interest in discovering and developing novel anti-cancer agents that can inhibit glutamine utilization. We have shown in our preclinical studies that the cell lines most sensitive to glutamine withdrawal are also the most sensitive to glutaminase inhibitors. Glutaminase is highly expressed in glutamine-dependent cancer cells and is more highly expressed in many human tumors than in normal tissues.

Glutaminase converts glutamine to glutamate, an amino acid required by cells for several essential functions. Many cancer cells, unlike normal cells, are dependent upon the enzyme glutaminase to make sufficient amounts of glutamate to grow and survive. This higher dependency upon the glutaminase pathway is likely due to an alternate use of the tricarboxylic acid, or TCA, cycle in cancer cells. The TCA cycle, which is sometimes referred to as the Krebs cycle, is a set of chemicals and chemical reactions that cells use to generate energy. Glutaminase inhibition in tumors implanted in animals leads to marked reduction in downstream metabolic intermediates including amino acids, nucleotides and glutathione. This supports our hypothesis that inhibitors of glutaminase can selectively target tumor cells by virtue of their increased dependence on glutaminase to convert glutamine to glutamate to resupply the TCA cycle, which is necessary to support growth and survival.

Dysregulated growth factor receptors and associated downstream signaling pathways in tumor cells are known to act in part to increase glucose utilization. Since these pathways are the targets of a number of approved targeted cancer therapeutic agents, we believe it is possible to rationally combine such agents with a glutaminase inhibitor to block the two main nutrients that promote cancer cell growth, thereby providing an enhanced therapeutic benefit.

As part of the mechanism for mounting an effective immune response, activated T-cells switch their metabolism to enable rapid proliferation. During this period of expansion, T-cell metabolism resembles the metabolism of cancer cells, and the need for both glucose and glutamine increases markedly. The expression of the checkpoint PD-1 on T-cells following activation inhibits the uptake and utilization of glucose and blocks rapid proliferation. The checkpoint inhibitors that block PD-L1 or PD-1 restore the ability of T-cells to utilize glucose. However, T-cells require both glucose and glutamine to proliferate. When tumor-bearing animals are treated with CB-839, there is a 4-8-fold increase in tumor levels of glutamine. We believe that this accumulation of glutamine has the indirect effect of supplying T-cells and NK cells with a needed nutrient. Since T-cell proliferation, unlike cancer cell proliferation, is not strongly inhibited by CB-839, we believe that combining CB-839 with inhibitors of the PD-L1/PD-1 checkpoint will support the full activation and expansion of cytotoxic immune cells in the nutrient-deprived tumor microenvironment and enhance anti-tumor responses.

Our Glutaminase Inhibitor CB-839

CB-839 is a potent, selective, reversible and orally bioavailable inhibitor of human glutaminase. CB-839 binds to a unique site on glutaminase that is distinct from the site that binds glutamine, thereby reducing the potential for undesirable side effects due to inhibition of other enzymes and receptors that bind glutamine. In our preclinical studies, CB-839 has been shown to halt the growth of or kill cancer cells across a range of tumor types. The compound has demonstrated antitumor activity in several different tumor models in animals. In addition, CB-839 has shown strong synergy with immunomodulatory agents and several kinase inhibitors that target growth factor pathways. In preclinical toxicology studies, CB-839 was well tolerated in animals at doses above those shown to

inhibit tumor growth. CB-839 has been well-tolerated in Phase 1 studies when administered as a single agent and has shown objective

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responses in renal cell cancer and acute myeloid leukemia. We believe that CB-839 is the only selective glutaminase inhibitor currently in clinical trials.

Preclinical Activity of CB-839

In our preclinical studies, CB-839 demonstrated antiproliferative and cell killing activity across a panel of tumor cell lines. This same panel of cell lines was also tested for growth or cell death when glutamine was removed from the incubation medium. There was a strong correlation between the response to CB-839 and the effect of glutamine withdrawal. We believe that these results provide evidence for the critical role of glutaminase in the utilization of glutamine to drive tumor cell growth and survival. We also evaluated the metabolic changes that resulted from inhibition of glutaminase in the same panel of cell lines. In the glutamine-dependent cancer cells treated with CB-839, the conversion of glutamine to glutamate was blocked, leading to the accumulation of glutamine and the depletion of glutamate. The loss of cellular glutamate further results in a reduction in downstream metabolites that provide energy and building blocks for the cell, including TCA cycle intermediates, amino acids, and the antioxidant glutathione. We believe that the reduction of the level of these and other metabolites is responsible for the anti-tumor activity observed with CB-839. In tumors implanted in animals, we also observed a 4-8-fold increase in the tumor concentration of glutamine, the substrate of glutaminase. Because many tumor cells consume large quantities of glutamine, an important nutrient for T-cells and NK cells, the tumor microenvironment is thought to be severely depleted of this nutrient. We believe that T-cells and NK cells benefit indirectly from treatment with CB-839 by the increased availability of glutamine in the tumor microenvironment.

At plasma concentrations of CB-839 of 300 nM or above, maximal effects on glutamine and glutamate levels in tumors were observed. In contrast, normal tissues in the same animals showed only small changes in the levels of glutamine and glutamate, despite exposure to high levels of CB-839. We believe that normal cells and tissues can utilize other pathways to produce glutamate, whereas most tumor cells have been genetically re-wired to be highly reliant on glutaminase as their principal source of glutamate. This provides a potential explanation for why high doses of CB-839 are well-tolerated in animals.

In addition to showing single agent activity across a wide range of cells from different tumor types, CB-839 also acted synergistically when combined with drugs that target the Ras/Raf and PI3K/mTOR branches of growth factor signaling pathways. The two agents acting together have a greater effect on the growth and survival of tumor cells than either agent used separately. CB-839 was synergistic with the epidermal growth factor receptor, or EGFR, inhibitor erlotinib (marketed as Tarceva) in NSCLC cells, with the multikinase inhibitors sunitinib (marketed as Sutent), sorafenib (marketed as Nexavar), trametinib (marketed as Mekinist), selumetinib (in development), pazopanib (marketed as Votrient), and cabozantinib (marketed as Cabometyx) and the mTOR inhibitors everolimus (marketed as Afinitor) and temsirolimus (marketed as Toricel) in renal cell carcinoma, or RCC, cells, and with the MEK inhibitor trametinib (marketed as Mekinist) and the AKT inhibitor MK-2206 (in development by Merck) in multiple cancer cell types. We believe these synergistic activities likely result from the fact that growth factor pathways control tumor metabolism and ultimately tumor cell dependence on glutamine and glucose.

CB-839 also acted synergistically when combined with I-O drugs that inhibited the PD-1/PD-L1 immune cell checkpoint. CB-839 significantly increased the number of tumor regressions observed in syngeneic mice bearing CT-26 colorectal tumors when used in combination with an anti-PD-1 checkpoint inhibitor, as shown in the figure below. Similar activity was observed when an anti-PD-L1 checkpoint inhibitor was used in combination with CB-839. These results are consistent with in vitro studies on T-cells indicating that high levels of both glucose and glutamine are required for full activation and proliferation of T-cells. Anti PD-1 is known to increase glucose utilization in T-cells, and we believe that CB-839, by blocking tumor consumption of glutamine, increases the concentration of glutamine in the tumor microenvironment to further activate and stimulate the proliferation of T-cells and NK cells.

In investigational new drug (IND) enabling toxicity studies in rats and monkeys, CB-839 was well tolerated in both species, with no dose limiting toxicities observed in either study. The plasma concentration of CB-839 measured at the highest dose in rats in these studies was greater than ten-fold above the 300 nM concentration required in mice to achieve maximal effects on glutamine and glutamate levels in tumors and suppress tumor growth. In independent studies, CB-839 was shown to distribute broadly to all tissues except the brain, indicating that glutaminase could be strongly inhibited in normal tissues without causing any major toxicological effects.

In February 2014, we initiated three Phase 1 clinical trials to assess the safety and tolerability of CB-839 in patients with solid and hematological tumors. CX-839-001 enrolled patients with solid tumors, CX-839-002 enrolled patients with multiple myeloma or non-Hodgkin's lymphoma, and CX-839-003 enrolled patients with acute myeloid or acute lymphocytic leukemia. As of the fourth quarter of 2016, we enrolled more than 240 patients across the three trials, including 160 patients who received CB-839 as a single agent, and 86 patients who received CB-839 in combination with other agents. Most patients in these trials were relapsed and refractory to multiple approved therapies. Drug concentration generally increased with dose, and increasing concentrations of CB-839 in blood were correlated with increasing inhibition of glutaminase in blood platelets. The half-life of CB-839 in blood was approximately four hours, and dosing with food enabled the dose schedule to be modified to a BID (twice-daily) regimen. The CX-839-002 and CX-839-003 studies are no longer enrolling patients and have been completed.

CB-839 has been generally well tolerated using doses up to 1000 mg. The primary treatment-related toxicities with monotherapy CB-839 that have been observed to date on the CX-839-001 study include fatigue, gastrointestinal events (nausea, vomiting, and constipation), elevations in liver function tests (LFTs) and photophobia. The majority of these adverse events have been mild to moderate (Grade 1/2) in severity. Treatment-related elevations in LFTs have generally been asymptomatic and rapidly reversible upon holding study treatment; the frequency of Grade 3 or greater occurrences have been reduced following the implementation of BID administration compared to the three times daily (TID) schedule. A similar safety profile has been observed on the CX-839-002 and -003 trials with the exception of a greater incidence of treatment emergent hematological toxicities, generally not considered treatment related.

Renal Cell Carcinoma (RCC)

According to the National Cancer Institute, renal cell carcinoma is diagnosed in approximately 62,700 people each year in the United States. Approximately 50% of renal cell carcinoma patients will require chemotherapy at some point to treat their metastatic disease. Clear cell is the most common form of kidney cancer comprising 75%-85% of cases. Most patients with clear cell RCC lack the tumor suppressor gene VHL. Preclinical studies by academic researchers have shown that VHL-deficient cell lines have an increased requirement for glutamine due to a loss of ability to make fatty acids from glucose. Accordingly, we believe that most patients with RCC tumors will have increased susceptibility to inhibition of glutaminase with CB-839. In RCC cell lines and in animal studies with human RCC tumors implanted in immunocompromised mice, we have demonstrated both single agent activity of CB-839 and activity in combination with approved multi-kinase inhibitors and mTOR inhibitors. CB-839 itself also induces suppression the nutrient-sensing mTOR pathway, likely due to a reduction in cellular amino acids and other key nutrients.

CB-839 was evaluated as a monotherapy in an RCC cohort in the dose expansion stage of our solid tumor Phase 1 clinical trial CX-839-001. As of December 31, 2016, 20 efficacy-evaluable RCC patients were treated with single agent CB-839 on the BID dosing schedule. One patient achieved a partial response with a substantial decrease in target lesions (32%), including a dramatic improvement in the patient's extensive lymphadenopathy. A total of 10 patients (50%) showed stable disease or better.

CB-839 is also being evaluated in expansion cohorts in combination with everolimus and cabozantinib. In November 2016, we presented data on 15 evaluable renal cell carcinoma patients treated with CB-839 in combination with everolimus, including 12 clear cell patients, and three papillary patients. 93% had disease control (response or stable disease); one patient had a partial response, one patient had progressive disease, and 13 patients have stable disease. The median progression free survival was 8.5 months and for the majority of patients, their time on therapy was longer than their time on treatment on immediate prior therapy. In the clear cell patient population the disease control rate was 100% and eight patients remained on study. Patients enrolled in the trial had advanced or metastatic disease and had received a median of two prior treatments, which included tyrosine kinase inhibitors, mTOR inhibitors, and checkpoint inhibitors. Patients were administered CB-839 in oral doses that ranged from 400-800 mg twice a day in combination with a fixed oral dose of everolimus at 10 mg once a day. The addition of CB-839 to full-dose everolimus has been well tolerated, with a similar safety profile to the known profile of everolimus alone. Grade 3 events include two events of hyperglycemia and one event each of diarrhea, anemia and fatigue.

We continue to enroll patients in this combination cohort, as well as a cohort of patients dosed with CB-839 in combination with cabozantinib. A randomized phase 2 trial of CB-839 in combination with everolimus is planned, and expected to initiate in the second half of 2017.

Triple-Negative Breast Cancer (TNBC)

According to the American Cancer Society, over 250,000 new cases of invasive breast cancer will be diagnosed in the United States and approximately 40,000 women will die from the disease in 2017. Between 10% and 20% of newly diagnosed cases of breast cancer are classified as triple-negative breast cancer. TNBC is a subset of breast cancer that lacks the estrogen receptor, the progesterone receptor, and the HER2 receptor. TNBC patients have relatively few treatment options since they lack expression of the targets for hormone- and HER2-based therapeutics. TNBC tends to have a higher rate of metastasis, recurs sooner following first line treatment and has a poorer prognosis and a lower overall survival rate than other subtypes of breast cancer. The incidence of TNBC is higher among African American women.

In preclinical studies, sensitivity to CB-839 in TNBC cells was directly correlated with the level of glutaminase expression and glutamine utilization. CB-839 had anti-tumor activity as a single agent against human breast cancer tumors implanted in animals, and in combination with paclitaxel, CB-839 enhanced activity and prevented the re-growth of the tumor following discontinuation of paclitaxel dosing. Higher glutamine utilization has also been observed in estrogen receptor negative tumors relative to estrogen receptor positive tumors, and in tumor tissue from patients of African ancestry relative to tumor tissue from patients of European ancestry.

In the Phase 1 trial CX-839-001, we enrolled an expansion cohort of refractory TNBC patients treated with CB-839 as a single agent and an additional cohort of refractory patients treated with CB-839 in combination with paclitaxel. In the monotherapy cohort, one patient showed a 23% decrease in target lesions and has remained on study for over 15 months.

In December 2016, we presented data on 28 triple negative breast cancer patients treated with doses of CB-839 of 400, 600 or 800 mg bid in combination with 80 mg/m² IV paclitaxel, weekly, three weeks out of four; 23 were evaluable for response. The majority of patients had received at least three prior lines of therapy, with 43% of patients treated with five or more prior therapies in the advanced/metastatic setting. Most patients had received prior taxane therapy in either the neo-adjuvant or metastatic setting. Among evaluable patients treated with CB-839 doses of at least 600 mg bid (n=16), there are 5 partial responses (31%) and disease control in 11 patients (69%). In addition, the combination overcame resistance to paclitaxel in heavily pretreated TNBC patients. There was a 38% response rate and 50% disease control rate in patients who received prior taxanes in the metastatic setting. There was a 50% response rate among taxane-refractory African American patients, consistent with higher glutamine utilization observed in tumors from this population. We plan to initiate a Phase 2 trial in triple negative breast cancer in the second half of 2017.

Immuno-Oncology Evaluation of CB-839 with Nivolumab

Cell lines and tumors that are treated with CB-839 in vitro or in vivo, respectively, have been shown to have a substantial increase in the content of glutamine. We believe that inhibition of glutaminase in the tumor results in a substantial increase in the concentration of glutamine in the tumor microenvironment and that this glutamine supports the growth and proliferation of cytotoxic T-cells and NK cells that reside within the tumor. Combination of CB-839 with anti-PD-1 or anti-PD-L1 in mice results in a doubling of the number of animals with complete tumor regressions.

In August 2016 we initiated CX-839-004, a Phase 1/2 clinical trial of CB-839 in combination with the PD-1 inhibitor nivolumab which in patients with RCC, melanoma, and NSCLC. The Phase 1/2 study will assess the safety, pharmacokinetics and pharmacodynamics of CB-839 and nivolumab. The study will enroll patients who are either naïve to checkpoint inhibitors, or were recently treated with nivolumab without tumor response. In December, 2016, we announced a clinical trial collaboration to evaluate Bristol-Myers Squibb's Opdivo in combination with CB-839 in patients with clear cell renal cell carcinoma. We expect to present data from this trial in the second half of 2017.

PIK3CA-mutated Colorectal Carcinoma (CRC)

The oncogene PIK3CA, which encodes the p110 catalytic subunit of phosphatidylinositol-3-kinase, is one of the most frequently mutated oncogenes in human cancers. Mutations in PIK3CA are found in approximately 10-20% CRC, which will result in between 13,000 and 26,000 new cases diagnosed in the United States in 2017.

An academic research group at Case Western Reserve University demonstrated that single agent CB-839 inhibits the growth of CRCs with PIK3CA mutations in immunocompromised mice, but CRC tumors with a normal PIK3CA gene were not inhibited. Remarkably, the combination of CB-839 with 5-fluorouracil induced complete and long-lasting tumor regressions in animals bearing PIK3CA mutant CRC tumors, but not tumors with normal PIK3CA, suggesting that this combinational therapy may be a unique and effective approach in the clinic. In the third quarter of 2016, an investigator-sponsored clinical trial was initiated by Drs. Jennifer Eads, Alok Khorana, and Neal Meropol at the Case Western Comprehensive Cancer Center. Enrollment in this study is ongoing.

Our Arginase Inhibitor Program

Tumors have evolved a number of strategies to avoid recognition and destruction by the immune system. One key mechanism is through suppression of cytotoxic T-cells that would otherwise attack and kill the cancer cells. Arginine is an amino acid that is fundamental to the function of cytotoxic T-cells. Without arginine, tumor specific cytotoxic T-cells fail to activate, proliferate, and mount an effective anti-tumor response.

In response to tumor-secreted factors, myeloid-derived suppressor cells, or MDSCs, and neutrophils accumulate in the tumor and secrete the enzyme arginase, resulting in depletion of arginine from the tumor microenvironment. Significant infiltration by arginase-expressing myeloid cells has been observed in many solid tumor types including lung, colorectal esophageal, bladder, head and neck, kidney cancer, and other tumor types. We have confirmed that arginase-expressing MDSCs are found by immunohistochemistry, or IHC, in a wide range of tumor types including non-small cell lung (both adenocarcinoma and squamous types), gastrointestinal and bladder cancers as shown in the diagram below. Arginase enzyme levels are elevated in the plasma of cancer patients across a wide range of malignancies.

We believe that arginase inhibitors can promote an anti-tumor immune response by restoring arginine levels, thereby allowing activation of the body's cytotoxic T-cells. A similar process exists whereby cytotoxic T-cells are blocked from activation through depletion of the amino acid tryptophan. Indoleamine 2,3-dioxygenase, or IDO, a tryptophan metabolizing enzyme, depletes tryptophan from the tumor microenvironment resulting in suppression of T-cell function. Several clinical trials of IDO inhibitors are currently ongoing and early clinical results with epacadostat (an IDO inhibitor from Incyte Corporation) have demonstrated combination activity with ipilimumab (anti CTLA-4) and anti-PD-1 antibodies.

We have identified CB-1158 and a portfolio of other small molecule arginase inhibitors that show high potency and oral bioavailability. In January, we announced that we entered into a global collaboration and license agreement for the research, development and commercialization of our small molecule arginase inhibitor CB-1158 in hematology and oncology with Incyte Corporation. Calithera and Incyte will collaborate on and co-fund the development of CB-1158 for oncology and hematology indications, with Incyte bearing 70% and Calithera bearing 30% of global development costs, unless Calithera opts out of development co-funding. Calithera will have the right to conduct a portion of clinical development studies under the collaboration, including combination studies of a licensed product with a proprietary compound of Calithera. If Calithera does not opt out of development co-funding, the parties will share profits and losses in the U.S., with 60% to Incyte and 40% to Calithera, and Calithera will have the right to co-detail licensed products in the U.S. Calithera retains rights to certain arginase inhibitors for specific indications outside of hematology and oncology.

CB-1158 has single agent anti-tumor activity in syngeneic mouse tumor models that has been demonstrated to act through an immune mechanism. The compound reduces the growth rate of mouse melanoma and lung tumors in immunocompetent mice when

administered as a single agent. CB-1158 also enhances the activity of checkpoint inhibitors in the mouse breast cancer 4T1 model. In this model, checkpoint inhibitors including anti-PD-1 and anti-CTLA-4 have no effect even when administered together. CB-1158 has anti-tumor activity in this model when added to a combination of anti-PD-1 and anti-CTLA-4; furthermore, we observed a 75% decrease in the number of lung metastases that were observed when CB-1158 was added to this regimen.

Inhibition of tumor growth was accompanied by an increase in the local concentration of arginine, and the induction of multiple pro-inflammatory changes in the tumor microenvironment. Treatment with CB-1158 also enhanced the anti-tumor activity of adoptive T-cell therapy, checkpoint blockade and chemotherapy in animal models.

CB-1158 entered clinical trials in September 2016, and is currently being tested in a Phase 1 clinical trial in patients with solid tumors. Three patients in the first cohort were treated with 50 mg of CB-1158 twice daily. This dose was well-tolerated and was pharmacologically active, resulting in sustained elevation of arginine in the plasma of all three patients. The trial is continuing to enroll patients in the dose escalation phase of the study, to be followed by combination studies with a PD-1 antibody. We plan to present additional data from the Phase 1 trial of CB-1158 in mid-2017.

We believe that CB-1158 is the only arginase inhibitor in clinical development.

In January 2017, we entered into a collaboration and license agreement, or the Incyte Collaboration Agreement, with Incyte Corporation. Under the terms of the Incyte Collaboration Agreement, we granted Incyte an exclusive, worldwide license to develop and commercialize its small molecule arginase inhibitors for hematology and oncology indications. The parties will collaborate on and co-fund the development of the licensed products, with Incyte bearing 70% and us bearing 30% of global development costs. The parties will share profits and losses in the U.S., with 60% to Incyte and 40% to us. We will have the right to co-detail the licensed products in the U.S, and Incyte will pay us tiered royalties ranging from the low to mid-double digits on net sales of licensed products outside the U.S. We may opt out of its co-funding obligation, in which case the U.S. profit sharing will no longer be in effect, and Incyte will pay us tiered royalties ranging from the low to mid-double digits on net sales of licensed products both in the U.S. and outside the U.S., and additional royalties to reimburse us for previously incurred development costs.

In December 2014, we entered into an exclusive license agreement, or the Arginase License Agreement, with Mars, Inc., by and through its Mars Symbioscience division, or Symbioscience, under which we have been granted the exclusive, worldwide license rights to develop and commercialize Symbioscience's portfolio of arginase inhibitors for use in human healthcare. Under the Arginase License Agreement, we are responsible for the worldwide development and commercialization of the licensed products at our cost, are required to use commercially reasonable efforts with respect to such development and commercialization activities, and must meet certain general diligence obligations. We hold the first right to prosecute and to enforce all licensed rights under the Arginase Licenses Agreement throughout the world, and Symbioscience will retain certain step-in enforcement rights. Under the exclusivity provisions of the Arginase License Agreement, each party agrees not to develop any other arginase inhibitors for use in human healthcare outside of the scope of the Arginase License Agreement.

Intellectual Property

Our commercial success depends in large part on our ability to obtain and maintain intellectual property protection for our product candidates, including CB-839, CB-1158, and our preclinical compounds, and our core technologies. Our policy is to seek to protect our intellectual property position by, among other methods, filing U.S. and foreign patent applications related to the technology, inventions and improvements that are important to the development and implementation of our business strategy. We also rely on trade secrets, know-how and continuing technological innovation to develop and maintain our proprietary position.

We file patent applications directed to our product candidates, preclinical compounds and related technologies to establish intellectual property positions on these compounds and their uses in disease. We are seeking patent protection for the use of biomarkers to identify patients most likely to benefit from treatment with our product candidates. As of December 31, 2016, we owned two issued U.S. patents, three issued foreign patents, and approximately 98 pending U.S. and foreign patent applications in the following foreign jurisdictions: Argentina, Australia, Brazil, Canada, China, the Eurasian Patent Organization, Europe, Hong Kong, India, Israel, Japan, Mexico, New Zealand, Singapore, South Africa, South Korea and Taiwan. We expect that these patents and patent applications, if issued, would expire between April 2031 and December 2037.

As of December 31, 2016, the intellectual property portfolio for our glutaminase inhibitor program, which includes CB-839, included two issued U.S. patents, both of which expire in 2032, claiming compositions of matter for and methods of treating cancer with CB-839. We also have three issued foreign patents, thirteen pending U.S. patent applications and 72 corresponding pending PCT and foreign patent applications directed to compositions of matter for CB-839 and related chemical compounds, as well as methods of using these compounds. These pending patent applications also include three pending U.S. patent applications relating to methods for measuring various biomarkers in cancer patients to identify patients suitable for treatment with glutaminase inhibitors. We expect that these patents and patent applications, if issued, would expire between November 2032 and August 2037.

The intellectual property portfolio for our arginase inhibitor program, which includes CB-1158, includes issued patents and pending patent applications that we have exclusively licensed from Symbioscience as well as pending patent applications that we own.

This portfolio includes 5 issued U.S. patents, 10 pending U.S. patent applications, 42 corresponding pending foreign patent applications, and 15 issued foreign patents directed to various arginase inhibitors and therapeutic methods of using the compounds. We expect that these patents and patent applications, if issued, would expire between April 2031 and December 2037.

Manufacturing

We do not own or operate, and currently have no plans to establish, any manufacturing facilities. We currently rely, and expect to continue to rely, on third parties to manufacture clinical supplies of CB-839 and CB-1158. CB-839 and CB-1158 are organic compounds of low molecular weight. Our third-party contract manufacturers are currently producing CB-839 and CB-1158 for use in our clinical trials utilizing reliable and reproducible synthetic processes and common manufacturing techniques. We obtain our supplies from manufacturers on a purchase order basis and do not have any long-term arrangements. In addition, we do not currently have arrangements in place for bulk drug substance or drug product services of CB-839 or CB-1158. We intend to identify and qualify additional manufacturers to provide bulk drug substance and drug product services prior to submission of a new drug application to the FDA if necessary to ensure sufficient commercial quantities of CB-839 and CB-1158.

Research and Development

We have and will continue to make substantial investments in research and development. Our research and development expenses totaled \$27.7 million, \$23.7 million, and \$16.4 million in 2016, 2015 and 2014, respectively.

In the ordinary course of business, we enter into agreements with third parties, such as contract research organizations, medical institutions, clinical investigators and contract laboratories, to conduct our clinical trials and aspects of our research and preclinical testing. These third parties provide project management and monitoring services and regulatory consulting and investigative services.

Competition

The pharmaceutical and biotechnology industries are characterized by rapidly advancing technologies, intense competition and a strong emphasis on proprietary products. While we believe that our technology, development experience and scientific knowledge provide us with competitive advantages, we face potential competition from many different sources, including major pharmaceutical, specialty pharmaceutical and biotechnology companies, academic institutions and governmental agencies and public and private research institutions. Any product candidates that we successfully develop and commercialize will compete with existing therapies and new therapies that may become available in the future.

Our principal competitors in the field of tumor metabolism include Advanced Cancer Therapeutics, LLC, Aeglea Biotherapeutics, Inc., Agios Pharmaceuticals, Inc., AstraZeneca plc, Bayer Pharma AG, Celgene Corporation, Cornerstone Pharmaceuticals, Inc., Eli Lilly and Company, Forma Therapeutics Holdings, LLC, GlaxoSmithKline plc, Merck KGaA, Novartis International AG, Pfizer Inc., Quantum Pharmaceuticals, 3-V Biosciences, Inc., Rhizen Pharmaceuticals SA, Roche Holdings, and its subsidiary Genentech Inc., Sprint Biosciences, and Takeda Pharmaceutical Co. Ltd. Our principal competitors in the field of tumor immunology include AstraZeneca plc, Boehringer Ingelheim GmbH, Bristol-Myers Squibb Company, CureTech Ltd., Eli Lilly and Company, Merck KGaA., Fortress Biotech, Inc., GlaxoSmithKline plc, Incyte Corporation, iTeos Therapeutics SA, Merck & Co., NewLink Genetics Corporation, Novartis International AG, Ono Pharmaceuticals, Co., Ltd, Pfizer Inc., Roche Holdings AG, Sanofi-aventis Groupe, Takeda Company Limited, and TG Therapeutics, Inc.

The most common methods of treating patients with cancer are surgery, radiation and drug therapy, including chemotherapy, hormone therapy and targeted drug therapy. There are a variety of available drug therapies marketed for cancer. In many cases, these drugs are administered in combination to enhance efficacy. Any product candidates we develop will compete with many existing drug and other therapies. To the extent they are ultimately used in combination with or as an adjunct to these therapies, our product candidates will not be competitive with them. Some of the currently approved drug therapies are branded and subject to patent protection, and others are available on a generic basis. Many of these approved drugs are well established therapies and are widely accepted by physicians, patients and third-party payors. In general, although there has been considerable progress over the past few decades in the treatment of cancer and the currently marketed therapies provide benefits to many patients, these therapies all are limited to some extent in their efficacy and frequency of adverse events, and none are successful in treating all patients. As a result, the level of morbidity and mortality from cancer remains high.

In addition to currently marketed therapies, there are also a number of therapeutics in late stage clinical development to treat cancer. These therapeutics in development may provide efficacy, safety, convenience and other benefits that are not provided by currently marketed therapies. As a result, they may provide significant competition for any product candidate for which we may obtain market approval.

Many of our competitors may have significantly greater financial resources and expertise in research and development, manufacturing, preclinical testing, conducting clinical trials, obtaining regulatory approvals and marketing approved therapeutics than we do. Mergers and acquisitions in the pharmaceutical, biotechnology and diagnostic 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 trial sites and patient registration for clinical trials, 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.

The key competitive factors affecting the success of CB-839, CB-1158, and any future product candidates we develop, if approved, are likely to be their efficacy, safety, synergy with other approved therapies, convenience, price and the availability of reimbursement from government and other third-party payors.

Our competitors may develop and commercialize therapeutics that are safer, more effective, have fewer or less severe side effects, are more convenient or are less expensive than any therapeutics that we may develop. Our competitors also may obtain FDA or other regulatory approval for their therapeutics 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, our ability to compete may be affected in many cases by insurers or other third-party and government programs seeking to control healthcare costs.

Government Regulation

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, manufacture, including any manufacturing changes, packaging, storage, recordkeeping, labeling, advertising, promotion, distribution, marketing, post-approval monitoring and reporting, import and export of pharmaceutical products, such as those we are developing.

United States Drug Approval Process

In the United States, the FDA regulates drugs under the Federal Food, Drug, and Cosmetic Act, or FDCA, and implementing regulations. The process of obtaining regulatory approvals and the subsequent compliance with appropriate federal, state, local and foreign statutes and regulations requires the expenditure of substantial time and financial resources. Failure to comply with the applicable United States requirements at any time during the product development process, approval process or after approval, may subject an applicant to a variety of administrative or judicial sanctions, such as the FDA's refusal to approve pending applications, withdrawal of an approval, imposition of a clinical hold, issuance of warning letters and untitled letters, product recalls, product seizures, total or partial suspension of production or distribution injunctions, fines, refusals of government contracts, restitution, disgorgement of profits or civil or criminal penalties.

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

- contract manufacturing expenses, primarily for the production of clinical supplies;
- completion of preclinical laboratory tests, animal studies and formulation studies in compliance with the FDA's good laboratory practice, or GLP, regulations;
- submission to the FDA of an IND, which must become effective before human clinical trials may begin;
- approval by an independent institutional review board, or IRB, at each clinical site before each trial may be initiated;
- performance of adequate and well-controlled human clinical trials in accordance with good clinical practices, or GCP, to establish the safety and efficacy of the proposed drug for each indication;

• submission to the FDA of a new drug application, or NDA;
• satisfactory completion of an FDA inspection of the manufacturing facility or facilities at which the product is produced to assess compliance with current good manufacturing practices, or cGMP, requirements and to assure that the facilities, methods and controls are adequate to preserve the drug's identity, strength, quality and purity; and
• FDA review and approval of the NDA.

Preclinical Studies and IND

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

must submit the results of the preclinical tests, together with manufacturing information, analytical data, any available clinical data or literature and plans for clinical trials, among other things, to the FDA as part of an IND. Some long-term preclinical testing, such as animal tests of reproductive adverse events and carcinogenicity, may continue after the IND is submitted. An IND automatically becomes effective 30 days after receipt by the FDA, unless before that time, the FDA raises concerns or questions related to one or more proposed clinical trials and places the trial on clinical hold. In such a case, the IND sponsor and the FDA must resolve any outstanding concerns before the clinical trial can begin. As a result, submission of an IND may not result in the FDA allowing clinical trials to commence.

Clinical Trials

Clinical trials involve the administration of the investigational new drug to human subjects under the supervision of qualified investigators in accordance with GCP requirements, which include, among other things, the requirement that all research subjects provide their informed consent in writing before their participation in any clinical trial. Clinical trials are conducted under written study protocols detailing, among other things, the objectives of the study, the parameters to be used in monitoring safety and the effectiveness criteria to be evaluated. A protocol for each clinical trial and any subsequent protocol amendments must be submitted to the FDA as part of the IND. In addition, an IRB at each institution participating in the clinical trial must review and approve the plan for any clinical trial before it commences at that institution, and the IRB must conduct continuing review. The IRB must review and approve, among other things, the study protocol and informed consent information to be provided to study subjects. An IRB must operate in compliance with FDA regulations. Information about certain clinical trials must be submitted within specific timeframes to the National Institutes of Health for public dissemination at www.clinicaltrials.gov. Human clinical trials are typically conducted in three sequential phases, which may overlap or be combined:

Phase 1: The drug is initially introduced into healthy human subjects or patients with the target disease or condition and tested for safety, dosage tolerance, absorption, metabolism, distribution, excretion and, if possible, to gain an early indication of its effectiveness.

Phase 2: The drug is administered to a limited patient population to identify possible adverse effects and safety risks, to preliminarily evaluate the efficacy of the product for specific targeted diseases and to determine dosage tolerance and optimal dosage.

Phase 3: The drug is administered to an expanded patient population in adequate and well-controlled clinical trials to generate sufficient data to statistically confirm the efficacy and safety of the product for approval, to establish the overall risk-benefit profile of the product and to provide adequate information for the labeling of the product.

Progress reports detailing the results of the clinical trials must be submitted at least annually to the FDA and, more frequently, if serious adverse events occur. Phase 1, Phase 2 and Phase 3 clinical trials may not be completed successfully within any specified period, or at all. Furthermore, the FDA or the sponsor may suspend or terminate a clinical trial at any time on various grounds, including a finding that the research subjects are being exposed to an unacceptable health risk. Similarly, an IRB can suspend or terminate approval of a clinical trial at its institution if the clinical trial is not being conducted in accordance with the IRB's requirements or if the drug has been associated with unexpected serious harm to patients.

Marketing Approval

Assuming successful completion of the required clinical testing, the results of the preclinical studies and clinical trials, together with detailed information relating to the product's chemistry, manufacture, controls and proposed labeling, among other things, are submitted to the FDA as part of an NDA requesting approval to market the product for one or more indications. Under federal law, the submission of most NDAs is additionally subject to a substantial application user fee, and the sponsor of an approved NDA is also subject to annual product and establishment user fees, which fees are typically increased annually.

The FDA conducts a preliminary review of all NDAs within the first 60 days after submission before accepting them for filing to determine whether they are sufficiently complete to permit substantive review. The FDA may request additional information rather than accept an NDA for filing. In this event, the application must be resubmitted with the additional information. The resubmitted application is also subject to review before the FDA accepts it for filing. Once the submission is accepted for filing, the FDA begins an in-depth substantive review. The FDA has agreed to specified performance goals in the review of NDAs. Under these goals, the FDA has committed to review most such applications for non-priority products within 10 months, and most applications for priority review products, that is, drugs that the FDA determines represent a significant improvement over existing therapy, within six months. The review process may be extended by the FDA for three additional months to consider certain information or clarification regarding information already provided in the submission. The FDA may also refer applications for novel drugs or 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. The FDA is not bound by the recommendations of an advisory committee, but it considers such recommendations carefully when making decisions.

Before approving an NDA, the FDA typically will inspect the facility or facilities where the product is manufactured. The FDA will not approve an application unless it determines that the manufacturing processes and facilities are in compliance with cGMP requirements and adequate to assure consistent production of the product within required specifications. In addition, before approving an NDA, the FDA will typically inspect one or more clinical sites to assure compliance with GCP and integrity of the clinical data submitted.

The testing and approval process requires substantial time, effort and financial resources, and each may take many years to complete. Data obtained from clinical activities are not always conclusive and may be susceptible to varying interpretations, which could delay, limit or prevent regulatory approval. The FDA may not grant approval on a timely basis, or at all. We may encounter difficulties or unanticipated costs in our efforts to develop our product candidates and secure necessary governmental approvals, which could delay or preclude us from marketing our products.

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

Fast Track Designation

The FDA is required to facilitate the development and expedite the review of drugs that are intended for the treatment of a serious or life-threatening condition for which there is no effective treatment and which demonstrate the potential to address unmet medical needs for the condition. Under the fast track program, the sponsor of a new product candidate may request the FDA to designate the product for a specific indication as a fast track product concurrent with or after the submission of the IND for the product candidate. The FDA must determine if the product candidate qualifies for fast track designation within 60 days after receipt of the sponsor's request.

In addition to other benefits, such as the ability of the sponsor to use surrogate endpoints in the evaluation of the pivotal clinical trials and have more frequent interactions with the FDA, the FDA may initiate review of sections of a fast track product's NDA before the application is complete. This rolling review is available if the applicant provides and the FDA approves a schedule for the submission of the remaining information and the applicant pays applicable user fees. However, the FDA's time period goal for reviewing a fast track application does not begin until the last section of the NDA is submitted. In addition, the fast track designation may be withdrawn by the FDA if the FDA believes that the designation is no longer supported by data emerging in the clinical trial process.

Priority Review

Under FDA policies, a product candidate may be eligible for priority review, or review generally within a six-month time frame from the time a complete application is received. Products regulated by the FDA's Center for Drug Evaluation and Research, or CDER, are eligible for priority review if they provide a significant improvement compared to marketed products in the treatment, diagnosis or prevention of a disease. A fast track designated product candidate would ordinarily meet the FDA's criteria for priority review.

Accelerated Approval

Under the FDA's accelerated approval regulations, the FDA may approve a drug for a serious or life-threatening illness that provides meaningful therapeutic benefit to patients over existing treatments based upon a surrogate endpoint that is reasonably likely to predict clinical benefit. In clinical trials, a surrogate endpoint is a measurement of laboratory or clinical signs of a disease or condition that substitutes for a direct measurement of how a patient feels, functions or survives. Surrogate endpoints can often be measured more easily or more rapidly than clinical endpoints. A product candidate approved on this basis is subject to rigorous post-

marketing compliance requirements, including the completion of Phase 4 or post-approval clinical trials to confirm the effect on the clinical endpoint. Failure to conduct required post-approval trials, or confirm a clinical benefit during post-marketing studies, would allow the FDA to withdraw the drug from the market on an expedited basis. All promotional materials for drug candidates approved under accelerated regulations are subject to prior review by the FDA.

Breakthrough Therapy Designation

Under the provisions of the Food and Drug Administration Safety and Innovation Act, or FDASIA, enacted in 2012, a sponsor can request designation of a product candidate as a “breakthrough therapy.” A breakthrough therapy is defined as a drug that is intended, alone or in combination with one or more other drugs, to treat a serious or life-threatening disease or condition, and preliminary clinical evidence indicates that the product candidate may demonstrate substantial improvement over existing therapies on one or more clinically significant endpoints, such as substantial treatment effects observed early in clinical development. Drugs designated as breakthrough therapies are also eligible for accelerated approval. The FDA must take certain actions, such as holding timely meetings and providing advice, intended to expedite the development and review of an application for approval of a breakthrough therapy. Even if a product candidate qualifies for one or more of these programs, the FDA may later decide that the product candidate no longer meets the conditions for qualification or decide that the time period for FDA review or approval will not be shortened.

Orphan Drugs

Under the Orphan Drug Act, the FDA may grant orphan drug designation to drugs intended to treat a rare disease or condition, which is generally defined as a disease or condition that affects fewer than 200,000 individuals in the United States. Orphan drug designation must be requested before submitting an NDA. After the FDA grants orphan drug designation, the generic identity of the drug and its potential orphan use are disclosed publicly by the FDA. Orphan drug designation does not convey any advantage in, or shorten the duration of, the regulatory review and approval process. The first NDA applicant to receive FDA approval for a particular active ingredient to treat a particular disease with FDA orphan drug designation is entitled to a seven-year exclusive marketing period in the United States for that product, for that indication. During the seven-year exclusivity period, the FDA may not approve any other applications to market the same drug for the same orphan indication, except in limited circumstances, such as a showing of clinical superiority to the product with orphan drug exclusivity in that it is shown to be safer, more effective or makes a major contribution to patient care. Orphan drug exclusivity does not prevent the FDA from approving a different drug for the same disease or condition, or the same drug 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 NDA application user fee.

Pediatric Exclusivity and Pediatric Use

Under the Best Pharmaceuticals for Children Act (BPCA) certain drugs may obtain an additional six months of exclusivity, if the sponsor submits information requested in writing by the FDA (a Written Request) relating to the use of the active moiety of the drug in children. The FDA may not issue a Written Request for studies on unapproved or approved indications or where it determines that information relating to the use of a drug in a pediatric population, or part of the pediatric population, may not produce health benefits in that population.

In addition, the Pediatric Research Equity Act (PREA) requires a sponsor to conduct pediatric studies for most drugs and biologics, for a new active ingredient, new indication, new dosage form, new dosing regimen or new route of administration. Under PREA, original NDAs, biologics license application and supplements thereto, must contain a pediatric assessment unless the sponsor has received a deferral or waiver. Unless otherwise required by regulation,

PREA does not apply to any drug for an indication where orphan designation has been granted. The required assessment must assess the safety and effectiveness of the product for the claimed indications in all relevant pediatric subpopulations and support dosing and administration for each pediatric subpopulation for which the product is safe and effective. The sponsor or FDA may request a deferral of pediatric studies for some or all of the pediatric subpopulations. A deferral may be granted for several reasons, including a finding that the drug or biologic is ready for approval for use in adults before pediatric studies are complete or that additional safety or effectiveness data needs to be collected before the pediatric studies begin. The FDA must send a non-compliance letter to any sponsor that fails to submit the required assessment, keep a deferral current or fails to submit a request for approval of a pediatric formulation.

Overview of FDA Regulation of Companion Diagnostics

We may seek to develop in vitro companion diagnostics for use in selecting the patients that we believe will respond to our therapeutics. In August 2014, the FDA issued a guidance document that states that if safe and effective use of a therapeutic product depends on an in vitro diagnostic, then the FDA generally will require approval or clearance of the diagnostic at the same time that the FDA approves the therapeutic product. The guidance addresses issues critical to developing and obtaining approval or clearance for

companion diagnostics and provide guidance as to when the FDA will require that the in vitro diagnostic, which is regulated as a medical device, and the drug be approved simultaneously. The FDA requires in vitro companion diagnostics intended to select the patients who will respond to cancer treatment to obtain approval simultaneously with approval of the drug.

Other Regulatory Requirements

Any drug manufactured or distributed by us pursuant to FDA approvals are subject to pervasive and continuing regulation by the FDA, including, among other things, requirements relating to recordkeeping, periodic reporting, product sampling and distribution, advertising and promotion and reporting of adverse experiences with the product. After approval, most changes to the approved product, such as adding new indications or other labeling claims are subject to prior FDA review and approval.

The FDA may impose a number of post-approval requirements, including REMs, as a condition of approval of an NDA. For example, the FDA may require post-marketing testing, including phase four clinical trials, and surveillance to further assess and monitor the product's safety and effectiveness after commercialization. Regulatory approval of oncology products often requires that patients in clinical trials be followed for long periods to determine the overall survival benefit of the drug.

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

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

Mitigation Strategy program. Other potential consequences include, among other things:

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

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

Additional Provisions

In addition to FDA restrictions on marketing of pharmaceutical products, several other types of state and federal laws have been applied to restrict certain marketing practices in the pharmaceutical industry in recent years. These laws include anti-kickback statutes and false claims statutes. The federal healthcare program anti-kickback statute prohibits, among other things, knowingly and willfully offering, paying, soliciting or receiving remuneration to induce or in return for purchasing, leasing, ordering or arranging for the purchase, lease or order of any healthcare item or service reimbursable under Medicare, Medicaid or other federally financed healthcare programs. This statute has been interpreted to apply to arrangements between pharmaceutical manufacturers on the one hand and prescribers, purchasers and formulary managers on the other. Violations of the anti-kickback statute are punishable by imprisonment, criminal fines, civil monetary penalties and exclusion from participation in federal healthcare programs. Although there are a number of statutory exemptions and regulatory safe harbors protecting certain common activities from prosecution or other regulatory sanctions, the exemptions and safe harbors are drawn narrowly, and practices that involve remuneration intended to induce prescribing, purchases or recommendations may be subject to scrutiny if they do not qualify for an exemption or safe harbor.

Federal false claims laws prohibit any person from knowingly presenting, or causing to be presented, a false claim for payment to the federal government, or knowingly making, or causing to be made, a false statement to have a false claim paid.

Recently, several pharmaceutical and other healthcare companies have been prosecuted under these laws for allegedly inflating drug prices they report to pricing services, which in turn were used by the government to set Medicare and Medicaid reimbursement rates, and for allegedly providing free product to customers with the expectation that the customers would bill federal programs for the product. In addition, certain marketing practices, including off-label promotion, may also violate false claims laws. The majority of states also have statutes or regulations similar to the federal anti-kickback law and false claims laws, which apply to items and services reimbursed under Medicaid and other state programs, or, in several states, apply regardless of the payor.

Foreign Regulation

In order to market any product outside of the United States, we would need to comply with numerous and varying regulatory requirements of other countries regarding safety and efficacy and governing, among other things, clinical trials, marketing authorization, commercial sales and distribution of our products. Whether or not we obtain FDA approval for a product, we would need to obtain the necessary approvals by the comparable regulatory authorities of foreign countries before we can commence clinical trials or marketing of the product in those countries. The approval process varies from country to country and can involve additional product testing and additional administrative review periods. The time required to obtain approval in other countries might differ from and be longer than that required to obtain FDA approval. Regulatory approval in one country does not ensure regulatory approval in another, but a failure or delay in obtaining regulatory approval in one country may negatively impact the regulatory process in others.

New Legislation and Regulations

From time to time, legislation is drafted, introduced and passed in Congress that could significantly change the statutory provisions governing the testing, approval, manufacturing and marketing of products regulated by the FDA. In addition to new legislation, FDA regulations and policies are often revised or interpreted by the agency in ways that may significantly affect our business and our products. It is impossible to predict whether further legislative changes will be enacted or whether FDA regulations, guidance, policies or interpretations changed or what the effect of such changes, if any, may be.

Employees

As of December 31, 2016, we had 50 full-time employees, including 21 employees with Ph.D. or M.D. degrees. Of these full-time employees, 37 employees are engaged in research and development activities. None of our employees are represented by a labor union or covered by a collective bargaining agreement.

Facilities

We occupy approximately 54,000 square feet of office and laboratory space in South San Francisco, California. Our lease term is through January 2024, with an option to extend another two years to January 2026. Approximately 21,000 square feet of laboratory space have been leased to another biotechnology company under a sublease agreement that expires in February 2020. We believe that our facility is sufficient to meet our current needs and that suitable additional space will be available as and when needed.

Legal Proceedings

From time to time, we may become involved in litigation relating to claims arising from the ordinary course of business. Our management believes that there are currently no claims or actions pending against us, the ultimate disposition of which could have a material adverse effect on our results of operations, financial condition or cash flows.

Item 1A. Risk Factors.

Our business involves significant risks, some of which are described below. You should carefully consider these risks, as well as other information in this Annual Report on Form 10-K, including our financial statements and the related notes and “Management’s Discussion and Analysis of Financial Condition and Results of Operations.” The occurrence of any of the events or developments described below could harm our business, financial condition, results of operations, cash flows, the trading price of our common stock and our growth prospects. Additional risks and uncertainties not presently known to us or that we currently deem immaterial may also impair our business operations.

Risks Related to Our Financial Position and Need For Additional Capital

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

Since our inception, we have incurred significant operating losses. Our net loss was \$38.0 million, \$32.6 million and \$21.7 million for 2016, 2015, and 2014, respectively. As of December 31, 2016, we had an accumulated deficit of \$122.5 million. To date, we have financed our operations primarily through private placements of our preferred stock, our initial public offering in October 2014, our at-the-market offering program and our global collaboration and license agreement with Incyte Corporation, or Incyte. We have devoted substantially all of our financial resources and efforts to research and development. We expect that it will be many years, if ever, before we receive regulatory approval and have a product candidate ready for commercialization. We expect to continue to incur significant expenses and increasing operating losses for the foreseeable future. Our net losses may fluctuate significantly from quarter to quarter and year to year. We anticipate that our expenses will increase substantially if and as we:

- advance further into clinical trials our existing clinical product candidates, CB-839 and CB-1158;
- continue the preclinical development of our research programs and advance candidates into clinical trials;
- identify additional product candidates and advance them into preclinical development;
- pursue regulatory approval of product candidates;
- seek marketing approvals for our product candidates that successfully complete clinical trials;
- establish a sales, marketing and distribution infrastructure to commercialize any product candidates for which we obtain marketing approval;
- maintain, expand and protect our intellectual property portfolio;
- hire additional clinical, regulatory and scientific personnel;
- add operational, financial and management information systems and personnel, including personnel to support product development;
- acquire or in-license other product candidates and technologies; and
- operate as a public company.

We have never generated any revenue from product sales and may never be profitable. To become and remain profitable, we and our collaborators must develop and eventually commercialize one or more products with significant market potential. This will require us to be successful in a range of challenging activities, including completing preclinical studies and clinical trials of our product candidates, obtaining marketing approval for these product candidates, manufacturing, marketing and selling those product candidates for which we may obtain marketing approval, and satisfying any post-marketing requirements. We may never succeed in these activities and, even if we do, may never generate revenue that is significant or large enough to achieve profitability. Our failure to become and remain profitable would decrease the value of the company and could impair our ability to raise capital, maintain our research and development efforts, expand our business or continue our operations. A decline in the value of our company could also cause you to lose all or part of your investment.

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

We expect our expenses to increase in connection with our ongoing activities, particularly as we continue the research and development of, continue and initiate clinical trials of and seek marketing approval for our product candidates, specifically CB-839 and CB-1158, and as we become obligated to make milestone payments pursuant to our outstanding license agreements. In addition, if

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we obtain marketing approval for any of our product candidates, we expect to incur significant commercialization expenses related to product sales, marketing, manufacturing and distribution of the approved product.

Our future capital requirements will depend on many factors, including:

- the scope, progress, results and costs of drug discovery, clinical development, laboratory testing and clinical trials for our product candidates, in particular CB-839 and CB-1158;
- the costs, timing and outcome of any regulatory review of our product candidates, CB-839 and CB-1158;
- the cost of any other product programs we pursue;
 - the costs and timing of commercialization activities, including manufacturing, marketing, sales and distribution, for any product candidates that receive marketing approval;
- the costs of preparing, filing and prosecuting patent applications, maintaining and enforcing our intellectual property rights and defending intellectual property-related claims;
- achieving the milestones set forth in our collaboration agreement with Incyte;
- our ability to establish and maintain collaborations on favorable terms, if at all; and
- the extent to which we acquire or in-license other product candidates and technologies.

Identifying potential product candidates and conducting preclinical studies and clinical trials are time consuming, expensive and uncertain processes that take years to complete, and we may never generate the necessary data or results required to obtain marketing approval and achieve product sales for any of our current or future product candidates. In addition, our product candidates, if approved, may not achieve commercial success. Our commercial revenue, if any, will be derived from sales of products that we do not expect to be commercially available for many years, if at all.

We do not have any material committed external source of funds or other support for our development efforts other than our collaboration agreement with Incyte for the development and commercialization of small molecule arginase inhibitors in hematology and oncology indications, including CB-1158, which agreement is terminable by Incyte for convenience or following our uncured breach. If Incyte terminates our collaboration agreement, we would need to obtain substantial additional sources of funding to develop CB-1158 as currently contemplated. If such additional funding is not available on favorable terms or at all, we may need to delay or reduce the scope of our CB-1158 development program or dedicate resources allocated to other programs to fund CB-1158. We may also need to grant rights in the United States, as well as outside the United States, to CB-1158 to one or more partners.

Accordingly, we will need substantial additional funding in connection with our continuing operations and to achieve our goals. We expect that our existing cash, cash equivalents, and investments will be sufficient to enable us to meet our current operating plan for at least the next 12 months. However, our existing cash, cash equivalents and investments may prove to be insufficient for these activities. If we are unable to raise capital when needed or on attractive terms, we would be forced to delay, reduce or eliminate our research and development programs or future commercialization efforts. Adequate additional financing may not be available to us on acceptable terms, or at all. In addition, we may seek additional financing due to favorable market conditions or strategic considerations, even if we believe we have sufficient funds for our operating plans.

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

Until such time, if ever, as we can generate substantial product revenue, we expect to finance our cash needs through a combination of equity and debt financings, as well as entering into new collaborations, strategic alliances and licensing arrangements. We do not have any committed external source of funds, other than our collaborations, which are limited in scope and duration. To the extent that we raise additional capital through the sale of equity or convertible debt securities, your ownership interest will be diluted, and the terms of these securities may include

liquidation or other preferences that adversely affect your rights as a common stockholder. Debt financing, if available, may involve agreements that include covenants limiting or restricting our ability to take specific actions, such as incurring additional debt, making capital expenditures or declaring dividends, and may be secured by all or a portion of our assets. If we raise funds by entering into new collaborations, strategic alliances or licensing arrangements in the future with third parties, we may have to relinquish valuable rights to our technologies, future revenue streams, research programs or product candidates or to grant licenses on terms that may not be favorable to us. If we are unable to raise additional funds through equity or debt financings or through collaborations, strategic alliances or licensing arrangements when needed, we may be required to delay, limit, reduce or terminate our product development or future commercialization efforts or grant rights to develop and market product candidates that we would otherwise prefer to develop and market ourselves.

Our short operating history may make it difficult for you to evaluate the success of our business to date and to assess our future viability.

We were founded in March 2010 and our operations to date have been limited to organizing and staffing our company, business planning, raising capital, developing our technology, identifying potential product candidates, undertaking preclinical studies and commencing Phase 1 clinical trials of our product candidate. CB-839 and CB-1158 are currently being evaluated in Phase 1 clinical trials. All of our other programs are in research and preclinical development. We have not yet demonstrated our ability to successfully complete any clinical trials, including large-scale, pivotal clinical trials required for regulatory approval of our product candidates, obtain marketing approvals, manufacture a commercial scale product, or arrange for a third party to do so on our behalf, or conduct sales and marketing activities necessary for successful commercialization. Typically, it takes many years to develop one new product from the time it is discovered to when it is commercially available. Consequently, any predictions made about our future success or viability may not be as accurate as they could be if we had a longer operating history or if we had product candidates in advanced clinical trials.

In addition, as a new business, we may encounter unforeseen expenses, difficulties, complications, delays and other known and unknown factors that may alter or delay our plans. We will need to transition from a company with a research focus to a company capable of supporting development activities and, if a product candidate is approved, a company with commercial activities. We may not be successful in any step in such a transition.

Risks Related to Drug Discovery, Development and Commercialization

Our approach to the discovery and development of product candidates that target tumor metabolism and tumor immunology is unproven and may never lead to marketable products.

Our scientific approach focuses on using our understanding of cellular metabolic pathways and the role of glutaminase and hexokinase in these pathways, as well as the role of arginase in the anti-tumor immune response, to identify molecules that are potentially promising as therapies for cancer indications. Any product candidates we develop may not effectively modulate metabolic or immunology pathways. The scientific evidence to support the feasibility of developing product candidates based on inhibiting tumor metabolism or impacting the anti-tumor immune response are both preliminary and limited. Although preclinical studies suggest that inhibiting glutaminase and hexokinase can suppress the growth of certain cancer cells, to date no company has translated this mechanism into a drug that has received marketing approval. Even if we are able to develop a product candidate in preclinical studies, we may not succeed in demonstrating the safety and efficacy of the product candidate in human clinical trials. Our expertise in cellular metabolic pathways, the role of glutaminase and hexokinase in these pathways, and the role of arginase in the anti-tumor immune response may not result in the discovery and development of commercially viable products to treat cancer.

We are very early in our development efforts, which may not be successful.

We have invested a significant portion of our efforts and financial resources in the identification of our most advanced product candidates, CB-839 and CB-1158, which are being evaluated in Phase 1 clinical trials. We have entered into a collaboration agreement with Incyte for the development and commercialization of CB-1158. Pursuant to our agreement, we collaborate on and co-fund the development of CB-1158 for hematology and oncology indications, with Incyte bearing 70% and Calithera bearing 30% of global development costs. All of our other programs are in research and preclinical development. It is also too early in our development efforts to determine whether our product candidates will demonstrate single-agent activity or will be developed for use in combination with other approved therapies, or both. As a result, the timing and costs of the regulatory paths we will follow and marketing approvals remain uncertain. Our ability to generate product revenue, which we do not expect will occur for many years, if ever,

will depend heavily on the successful development and eventual commercialization of CB-839 and CB-1158. The success of CB-839, CB-1158 and any other product candidates we may develop will depend on many factors, including the following:

- successful enrollment in, and completion of, clinical trials;
- demonstrating safety and efficacy;
- receipt of marketing approvals from applicable regulatory authorities;
- establishing commercial manufacturing capabilities or making arrangements with third-party manufacturers;
- obtaining and maintaining patent and trade secret protection and non-patent exclusivity for our product candidates;
- launching commercial sales of the product candidates, if and when approved, whether alone or selectively in collaboration with others;
- Our ability to successfully develop and commercialize small molecule arginase inhibitors, including CB-1158 with Incyte;
- acceptance of the product candidates, if and when approved, by patients, the medical community and third-party payors;

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- effectively competing with other therapies;
- a continued acceptable safety profile of the products following approval; and
- enforcing and defending intellectual property rights and claims.

If we do not accomplish one or more of these goals in a timely manner, or at all, we could experience significant delays or an inability to successfully commercialize our product candidates, which would harm our business.

We may not be successful in our efforts to identify or discover potential product candidates.

Our drug discovery efforts may not be successful in identifying compounds that are useful in treating cancer. Our research programs may initially show promise in identifying potential product candidates, yet fail to yield product candidates for clinical development for a number of reasons. In particular, our research methodology used may not be successful in identifying compounds with sufficient potency or bioavailability to be potential product candidates. In addition, our potential product candidates may, on further study, be shown to have harmful side effects or other negative characteristics.

Research programs to identify new product candidates require substantial technical, financial and human resources. We may choose to focus our efforts and resources on potential product candidates that ultimately prove to be unsuccessful. If we are unable to identify suitable compounds for preclinical and clinical development, we will not be able to generate product revenue, which would harm our financial position and adversely impact our stock price.

If clinical trials of our product candidates fail to demonstrate safety and efficacy to the satisfaction of regulatory authorities or do not otherwise produce positive results, we may incur additional costs or experience delays in completing, or ultimately be unable to complete, the development and commercialization of our product candidates.

Before obtaining marketing approval from regulatory authorities for the sale of our product candidates, we must complete preclinical development and in the case of CB-1158, together with Incyte, then conduct extensive clinical trials to demonstrate the safety and efficacy of our product candidates in humans. Clinical testing is expensive, difficult to design and implement, can take many years to complete and is uncertain as to outcome. A failure of one or more clinical trials could occur at any stage of testing. The outcome of preclinical testing and early clinical trials may not be predictive of the success of later clinical trials, and interim results of a particular clinical trial do not necessarily predict final results of that trial.

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

We may experience numerous unforeseen events during, or as a result of, preclinical testing or clinical trials that could delay or prevent our ability to receive marketing approval or commercialize our product candidates, including that:

- regulators or institutional review boards may not authorize us or our investigators to commence a clinical trial or conduct a clinical trial at a prospective trial site;
- we may have delays in reaching or fail to reach agreement on acceptable clinical trial contracts or clinical trial protocols with prospective trial sites;
- clinical trials of our product candidates may produce negative or inconclusive results, and we may decide, or regulators may require us, to conduct additional clinical trials or abandon product development programs;
- the number of patients required for clinical trials of our product candidates may be larger than we anticipate; enrollment in these clinical trials may be slower than we anticipate, or participants may drop out of these clinical trials at a higher rate than we anticipate;

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our third-party contractors may fail to comply with regulatory requirements or meet their contractual obligations to us in a timely manner, or at all;

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regulators or institutional review boards may require that we or our investigators suspend or terminate clinical research for various reasons, including noncompliance with regulatory requirements or a finding that the participants are being exposed to unacceptable health risks;

the cost of clinical trials of our product candidates may be greater than we anticipate; and

the supply or quality of our product candidates or other materials necessary to conduct clinical trials of our product candidates may be insufficient or inadequate.

If we are required to conduct additional clinical trials or other testing of our product candidates beyond those that we currently contemplate, if we are unable to successfully complete clinical trials of our product candidates or other testing, if the results of these trials or tests are not positive or are only modestly positive or if there are safety concerns, we may:

be delayed in obtaining marketing approval for our product candidates;

not obtain marketing approval at all;

obtain approval for indications or patient populations that are not as broad as intended or desired;

obtain approval with labeling that includes significant use or distribution restrictions or safety warnings, including boxed warnings;

be subject to additional post-marketing testing requirements; or

have the product removed from the market after obtaining marketing approval.

Product development costs will also increase if we experience delays in testing or in receiving marketing approvals.

We do not know whether any clinical trials will begin as planned, will need to be restructured or will be completed on schedule, or at all. Significant clinical trial delays also could shorten any periods during which we may have the exclusive right to commercialize our product candidates, could allow our competitors to bring products to market before we do, and could impair our ability to successfully commercialize our product candidates, any of which may harm our business and results of operations.

If we experience delays or difficulties in enrolling patients in clinical trials, our receipt of necessary regulatory approvals could be delayed or prevented.

We may not be able to initiate or continue clinical trials for our product candidates if we are unable to identify and enroll a sufficient number of eligible patients to participate in these trials as required by the U.S. Food and Drug Administration, or FDA, or analogous regulatory authorities outside the United States. In addition, some of our competitors may have ongoing clinical trials for product candidates that would treat the same indications as our product candidates, and patients who would otherwise be eligible for our clinical trials may instead enroll in clinical trials of our competitors' product candidates. Patient enrollment is also affected by other factors, including:

severity of the disease under investigation;

availability and efficacy of approved medications for the disease under investigation;

eligibility criteria for the trial in question;

perceived risks and benefits of the product candidate under study;

efforts to facilitate timely enrollment in clinical trials;

patient referral practices of physicians;

the ability to monitor patients adequately during and after treatment; and

proximity and availability of clinical trial sites for prospective patients.

Our inability to enroll a sufficient number of patients for our clinical trials would result in significant delays or may require us to abandon one or more clinical trials altogether. Enrollment delays in our clinical trials may result in increased development costs for our product candidates, which would cause the value of our company to decline and limit our ability to obtain additional financing.

If serious adverse effects or unexpected characteristics of our product candidates are identified during development, we may need to abandon or limit our development of some or all of our product candidates.

We are currently evaluating CB-839 and CB-1158 in Phase 1 clinical trials. All our other programs are in research and preclinical development and their risk of failure is high. It is impossible to predict when or if any of our product candidates will prove effective or safe in humans or will receive marketing approval. Adverse events or undesirable side effects caused by, or other unexpected properties of, our product candidates could cause us, any current or future collaborators, an institutional review board or regulatory authorities to interrupt, delay or halt clinical trials of one or more of our product candidates and could result in a more restrictive label, or the delay or denial of marketing approval by the FDA or comparable foreign regulatory authorities. If adverse effects were to arise in patients being treated with any of our product candidates, it could require us to halt, delay or interrupt clinical trials of such product candidate or adversely affect our ability to obtain requisite approvals to advance the development and commercialization of such product candidate. If our product candidates are associated with undesirable side effects or have characteristics that are unexpected, we may need to abandon their development or limit development to certain uses or subpopulations in which the undesirable side effects or other characteristics are less prevalent, less severe or more acceptable from a risk-benefit perspective. Many agents that initially showed promise in early stage testing for treating cancer or other diseases have later been found to cause side effects that prevented further development of the agent.

We are in early clinical trials with CB-839 and we have seen several adverse events deemed possibly or probably related to CB-839. As of November 2015, a variety of adverse events, or AEs, have been reported. In the CX839-001 study, treatment-emergent Grade ≥ 3 AEs occurring in $>5\%$ of patients included increases in liver enzymes aspartate aminotransferase (AST) and alanine aminotransferase (ALT). With a change to twice daily dosing with food, only one out of the 66 patients showed a Grade 3 liver enzyme increase. We have treated an insufficient number of patients to fully assess the safety of CB-839 and, as our trials progress, we may experience more frequent or more severe adverse events. Our ongoing and planned trials for CB-839 and our and Incyte's ongoing and planned trials for CB-1158 may fail due to safety issues, and we may need to abandon development of CB-839 or CB-1158. Our other research programs may fail due to preclinical or clinical safety issues, causing us to abandon or delay the development of a product candidate from these programs.

Results of preclinical studies and early clinical trials may not be predictive of results of future clinical trials.

The outcome of preclinical studies and early clinical trials may not be predictive of the success of later clinical trials, and interim results of clinical trials do not necessarily predict success in future clinical trials. Many companies in the pharmaceutical and biotechnology industries have suffered significant setbacks in late-stage clinical trials after achieving positive results in earlier development, and we could face similar setbacks. The design of a clinical trial can determine whether its results will support approval of a product and flaws in the design of a clinical trial may not become apparent until the clinical trial is well advanced. We may experience delays in designing and executing clinical trials to support marketing approval. In addition, preclinical and clinical data are often susceptible to varying interpretations and analyses. Many companies that believed their product candidates performed satisfactorily in preclinical studies and clinical trials have nonetheless failed to obtain marketing approval for the product candidates. Even if we, or our current and future collaborators, believe that the results of clinical trials for our product candidates warrant marketing approval, the FDA or comparable foreign regulatory authorities may disagree and may not grant marketing approval of our product candidates.

In some instances, there can be significant variability in safety or efficacy results between different clinical trials of the same product candidate due to numerous factors, including changes in trial procedures set forth in protocols, differences in the size and type of the patient populations, changes in and adherence to the dosing regimen and other clinical trial protocols and the rate of dropout among clinical trial participants. If we fail to receive positive results in

clinical trials of our product candidates, the development timeline and regulatory approval and commercialization prospects for our most advanced product candidates, and, correspondingly, our business and financial prospects would be negatively impacted.

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

We have limited financial and managerial resources. As a result, we may forego or delay pursuit of opportunities with other product candidates or for other indications that later prove to have greater commercial potential. Our resource allocation decisions may cause us to fail to capitalize on viable commercial products or profitable market opportunities. Our spending on current and future research and development programs and product candidates for specific indications may not yield any commercially viable 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 collaboration, licensing or other royalty arrangements, including our agreement with Incyte, in cases in which it would have been more advantageous for us to retain sole development and commercialization rights to such product candidate. In addition, under our agreement with Incyte, Incyte has the right to commercialize CB-1158 in hematology and oncology indications. If Incyte does not successfully commercialize CB-1158, we may be unable to realize the full value from our collaboration with Incyte.

Even if any of our product candidates receives marketing approval, we or others may later discover that the product is less effective than previously believed or causes undesirable side effects that were not previously identified, which could compromise our ability, or that of any future collaborators, to market the product.

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

- regulatory authorities may withdraw their approval of the product or seize the product;
- we, or any future collaborators, may be required to recall the product, change the way the product is administered or conduct additional clinical trials;
- additional restrictions may be imposed on the marketing of, or the manufacturing processes for, the particular product;
- we may be subject to fines, injunctions or the imposition of civil or criminal penalties;
- regulatory authorities may require the addition of labeling statements, such as a “black box” warning or a contraindication;
- we, or any future collaborators, may be required to create a Medication Guide outlining the risks of the previously unidentified side effects for distribution to patients;
- we, or any future collaborators, could be sued and held liable for harm caused to patients;
- the product may become less competitive; and
- our reputation may suffer.

Even if any of our product candidates receive marketing approval, they may fail to achieve the degree of market acceptance by physicians, patients, third party payors and others in the medical community necessary for commercial success.

If any of our product candidates receive marketing approval, they may nonetheless fail to gain sufficient market acceptance by physicians, patients, third party payors and others in the medical community for us to achieve commercial success. For example, current cancer treatments like chemotherapy and radiation therapy for certain diseases and conditions are well established in the medical community, and doctors may continue to rely on these treatments. If our product candidates do not achieve an adequate level of acceptance, we may not generate significant product revenue to become profitable. The degree of market acceptance of our product candidates, if approved for commercial sale, will depend on a number of factors, including:

- the efficacy and potential advantages compared to alternative treatments;
- our ability to offer any approved products for sale at competitive prices;
- convenience and ease of administration compared to alternative treatments;
- the willingness of the target patient population to try new therapies and of physicians to prescribe these therapies;
- the strength of marketing and distribution support;
- sufficient third-party coverage or reimbursement; and
- the prevalence and severity of any side effects.

If, in the future, we are unable to establish sales and marketing capabilities or to selectively enter into agreements with third parties to sell and market our product candidates, we may not be successful in commercializing our product candidates if and when they are approved.

We do not have a sales or marketing infrastructure and have no experience in the sale, marketing or distribution of pharmaceutical products. To achieve commercial success for any approved product for which we retain sales and marketing responsibilities, we must either develop a sales and marketing organization or outsource these functions to other third parties. For our small molecule arginase inhibitors in hematology and oncology indications, including CB-1158, unless we establish our own sales and marketing capabilities, we will be significantly dependent on Incyte's sales and marketing infrastructure to effectively commercialize these products. In the future, we may choose to build a focused sales and marketing infrastructure to sell some of our product candidates if and when they are approved.

There are risks involved both with establishing our own sales and marketing capabilities and with entering into arrangements with third parties to perform these services. For example, recruiting and training a sales force is expensive and time consuming and could delay any product launch. If the commercial launch of a product candidate for which we recruit a sales force and establish marketing capabilities is delayed or does not occur for any reason, we would have prematurely or unnecessarily incurred these commercialization expenses. This may be costly, and our investment would be lost if we cannot retain or reposition our sales and marketing personnel.

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

- our inability to recruit and retain adequate numbers of effective sales and marketing personnel;
- the inability of sales personnel to obtain access to physicians or persuade adequate numbers of physicians to prescribe any future products; and
- unforeseen costs and expenses associated with creating an independent sales and marketing organization.

If we enter into arrangements with third parties to perform sales, marketing and distribution services, our product revenue or the profitability of these product revenue to us may be lower than if we were to market and sell any products that we develop ourselves. In addition, we may not be successful in entering into arrangements with third parties to sell and market our product candidates or may be unable to do so on terms that are favorable to us. We may have little control over such third parties, and any of them may fail to devote the necessary resources and attention to sell and market our products effectively. If we do not establish sales and marketing capabilities successfully, either on our own or in collaboration with third parties, we will not be successful in commercializing our product candidates.

We face substantial competition, which may result in others discovering, developing or commercializing products before or more successfully than we do.

The development and commercialization of new drug products is highly competitive. Research and discoveries by others may result in breakthroughs which may render our products obsolete even before they generate any revenue. We face competition with respect to our current product candidates, and will face competition with respect to any product candidates that we may seek to develop or commercialize in the future, from major pharmaceutical companies, specialty pharmaceutical companies and biotechnology companies worldwide. There are a number of large pharmaceutical and biotechnology companies that currently market and sell products or are pursuing the development of products for the treatment of the cancer indications for which we are focusing our product development efforts. Some of these competitive products and therapies are based on scientific approaches that are the same as or similar to our approach and others are based on entirely different approaches. Potential competitors also include academic institutions, government agencies and other public and private research organizations that conduct research, seek patent protection and establish collaborative arrangements for research, development, manufacturing and commercialization.

We are developing our product candidates for the treatment of various cancers. There are a variety of available drug therapies marketed for cancer. In many cases, these drugs are administered in combination to enhance efficacy. Some of the currently approved drug therapies are branded and subject to patent protection, and others are available on a generic basis. Many of these approved drugs are well-established therapies and are widely accepted by physicians, patients and third-party payors. Insurers and other third-party payors may also encourage the use of generic products. We expect that if our product candidates are approved, they will be priced at a significant premium over competitive generic products. This may make it difficult for us to achieve our business strategy of using our product candidates in combination with existing therapies or replacing existing therapies with our product candidates.

There are also a number of product candidates in preclinical and clinical development by third parties to treat cancer by targeting cellular metabolism. Our principal competitors include Abbvie Inc., Advanced Cancer Therapeutics, LLC, Aeglea Biotherapeutics, Inc., Agios Pharmaceuticals, Inc., AstraZeneca plc, Bayer Pharma AG, Boehringer

Ingelheim GmbH, Bristol-Myers Squibb Company, Celgene Corporation, Cornerstone Pharmaceuticals, Inc., CureTech Ltd., Eli Lilly and Company, Forma Therapeutics Holdings, LLC, Fortress Biotech, Inc., GlaxoSmithKline plc, Incyte Corporation, iTeos Therapeutics SA, Merck & Co., Janssen Biotech, Inc., Merck KGaA, NewLink Genetics Corporation, Novartis International AG, Ono Pharmaceuticals, Co., Ltd, Pfizer Inc., Quantum Pharmaceuticals, 3-V Biosciences, Inc., Regeneron Pharmaceuticals, Inc., Rhizen Pharmaceuticals SA, Roche Holdings, and its subsidiary Genentech Inc., Sanofi-Aventis Groupe, Sprint Biosciences, Takeda Pharmaceutical Co. Ltd. and TG Therapeutics, Inc.

Our competitors may develop products that are more effective, safer, more convenient or less costly than any that we are developing or that would render our product candidates obsolete or non-competitive. In addition, our competitors may discover biomarkers that more efficiently measure metabolic pathways than our methods, which may give them a competitive advantage in developing potential products. Our competitors may also obtain marketing approval from the FDA or other regulatory authorities for

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

Even if we are able to commercialize any product candidates, these products may become subject to unfavorable pricing regulations, third-party reimbursement practices or healthcare reform initiatives, which would harm our business.

The regulations that govern marketing approvals, pricing and reimbursement for new drugs vary widely from country to country. In the United States, new and future legislation may significantly change the approval requirements in ways that could involve additional costs and cause delays in obtaining approvals. Some countries require approval of the sale price of a drug before it can be marketed. In many countries, the pricing review period begins after marketing or product-licensing approval is granted. In some foreign markets, prescription pharmaceutical pricing remains subject to continuing governmental control even after initial marketing approval is granted. As a result, we might obtain marketing approval for a drug in a particular country, but then be subject to price regulations that delay its commercial launch, possibly for lengthy time periods, and negatively impact the revenue we are able to generate from the sale of the drug in that country. Adverse pricing limitations may hinder our ability to commercialize and generate revenue from one or more product candidates, even if our product candidates obtain marketing approval.

Our ability to commercialize any product candidates successfully also will depend in part on the extent to which reimbursement for these products and related treatments will be available from government health programs, private health insurers and other organizations. Government authorities and third-party payors, such as private health insurers and health maintenance organizations, decide which medications they will pay for and establish reimbursement levels. A significant trend in the U.S. healthcare industry and elsewhere is cost containment. Government authorities and third-party payors have attempted to control costs by limiting coverage and the amount of payment for particular medications. Increasingly, third-party payors are requiring that drug companies provide them with predetermined discounts from list prices and are challenging the prices charged for medical products. Reimbursement may not be available for any product that we commercialize and, if reimbursement is available, the level of reimbursement may not be sufficient. Reimbursement may impact the demand for, or the price of, any product candidate for which we obtain marketing approval. If reimbursement is not available or is available only to limited levels, we may not be able to successfully commercialize any product candidate for which we obtain marketing approval.

There may be significant delays in obtaining reimbursement for newly approved products, and coverage may be more limited than the purposes for which the product is approved by the FDA or similar regulatory authorities outside the United States. Moreover, eligibility for reimbursement does not imply that any product will be paid for in all cases or at a rate that covers our costs, including research, development, manufacture, sale and distribution. Interim reimbursement levels for new drugs, if applicable, may also not be sufficient to cover our costs and may not be made permanent. Reimbursement rates may vary according to the use of the drug and the medical circumstances under which it is used, may be based on reimbursement levels already set for lower cost products or procedures or may be incorporated into existing payments for other services. Net prices for drugs may be reduced by mandatory discounts or rebates required by government healthcare programs or private payors and by any future relaxation of laws that presently restrict imports of drugs from countries where they may be sold at lower prices than in the United States.

Third-party payors often rely upon Medicare coverage policies and payment limitations in setting their own reimbursement policies. Our inability to promptly obtain coverage and profitable payment rates from both government-funded programs and private payors for any approved products that we develop could have a material adverse effect on our operating results, our ability to raise capital needed to commercialize our approved products and our overall financial condition.

Product liability lawsuits against us could cause us to incur substantial liabilities and could limit the commercialization of any product candidates we may develop.

We face an inherent risk of product liability exposure related to the testing of our product candidates in human clinical trials and will face an even greater risk if we commercially sell any products that we may develop after approval. If we cannot successfully defend ourselves against claims that our product candidates caused injuries, we could incur substantial liabilities. Regardless of merit or eventual outcome, liability claims may result in:

- decreased demand for any product candidates that we may develop;
- injury to our reputation and significant negative media attention;

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- withdrawal of clinical trial participants;
- significant costs to defend any related litigation;
- substantial monetary awards to trial participants or patients;
- loss of revenue; and
- the inability to commercialize any products we may develop.

Although we maintain product liability insurance coverage in the amount of up to \$10.0 million per claim and in the aggregate, it may not be adequate to cover all liabilities that we may incur. We anticipate that we will need to increase our insurance coverage as we continue clinical trials and if we successfully commercialize any products. Insurance coverage is increasingly expensive. We may not be able to maintain insurance coverage at a reasonable cost or in an amount adequate to satisfy any liability that may arise.

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

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

Although we maintain workers' compensation insurance to cover us for costs and expenses we may incur due to injuries to our employees in our workplace, including those resulting from the use of hazardous materials, this insurance may not provide adequate coverage against potential liabilities. We do not maintain insurance for environmental liability or toxic tort claims that may be asserted against us in connection with our storage or disposal of biological, chemical, hazardous or radioactive materials.

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

Risks Related to Our Dependence on Third Parties

We rely on third parties to conduct our clinical trials and some aspects of our research and preclinical testing, and those third parties may not perform satisfactorily, including failing to meet deadlines for the completion of such trials, research or testing.

We currently rely and expect to continue to rely on third parties, such as our collaborators, contract research organizations, clinical data management organizations, medical institutions and clinical investigators, to conduct our clinical trials and to conduct some aspects of our research and preclinical testing. Any of these third parties may terminate their engagements with us at any time. If these third parties do not successfully carry out their contractual duties, meet expected deadlines or conduct our clinical trials in accordance with regulatory requirements or our stated protocols, we will not be able to obtain, or may be delayed in obtaining, marketing approvals for our product candidates and will not be able to, or may be delayed in our efforts to, successfully commercialize our product candidates. Furthermore, these third parties may also have relationships with other entities, some of which may be our competitors. If we need to enter into alternative arrangements, it would delay our product development activities.

Our reliance on these third parties for research and development activities will reduce our control over these activities but will not relieve us of our responsibilities. For example, we will remain responsible for ensuring that each of our clinical trials is conducted in accordance with the general investigational plan and protocols for the trial. Moreover, the FDA requires us to comply with standards, commonly referred to as Good Clinical Practices, for conducting, recording and reporting the results of clinical trials to assure that data and reported results are credible and accurate and that the rights, integrity and confidentiality of trial participants are protected. We also are required to register ongoing clinical trials and post the results of completed clinical trials on a government sponsored database, available at www.clinicaltrials.gov, within certain timeframes. Failure to do so can result in fines, adverse publicity and civil and criminal sanctions.

We do not have any manufacturing facilities. We currently rely, and expect to continue to rely, on third party manufacturers for the manufacture of our product candidates for preclinical studies and clinical trials and for commercial supply of any of these product candidates for which we obtain marketing approval. To date, we have obtained or plan to obtain materials for CB-839 and CB-1158

for our current and planned clinical trials from third-party manufacturers. We have engaged third party manufacturers to obtain the active ingredient for CB-839 and CB-1158 for pre-clinical testing and clinical trials. We do not have a long-term supply agreement with any third-party manufacturers, and we purchase our required drug supply on a purchase order basis.

We may be unable to establish agreements with third-party manufacturers or to do so on acceptable terms. Even if we are able to establish agreements with third-party manufacturers, reliance on third-party manufacturers entails additional risks, including:

- reliance on the third party for regulatory compliance and quality assurance;
- the possible breach of the manufacturing agreement by the third party; and
- the possible termination or nonrenewal of the agreement by the third party at a time that is costly or inconvenient for us.

Third-party manufacturers may not be able to comply with current U.S. Good Manufacturing Practice requirements, or cGMPs, or similar regulatory requirements outside the United States. Our failure, or the failure of our third-party manufacturers, to comply with applicable regulations could result in sanctions being imposed on us, including fines, injunctions, civil penalties, delays, suspension or withdrawal of approvals, license revocation, seizures or recalls of product candidates, operating restrictions and criminal prosecutions, any of which could adversely affect supplies of our product candidates and harm our business and results of operations.

Any product that we may develop may compete with other product candidates and products for access to these manufacturing facilities. There are a limited number of manufacturers that operate under cGMPs and that might be capable of manufacturing for us.

Any performance failure on the part of our existing or future manufacturers could delay clinical development or marketing approval. We do not currently have arrangements in place for redundant supply for bulk drug substances. If any one of our current contract manufacturers cannot perform as agreed, we may be required to replace that manufacturer. Although we believe that there are several potential alternative manufacturers who could manufacture our product candidates, we may incur added costs and delays in identifying and qualifying any such replacement.

Our current and anticipated future dependence upon others for the manufacture of our product candidates or products may adversely affect our future profit margins and our ability to commercialize any product candidates that receive marketing approval on a timely and competitive basis.

We also currently rely, and expect to continue to rely, on third parties to store and distribute drug supplies for our clinical trials. Any performance failure on the part of these third parties could delay clinical development or marketing approval of our product candidates or commercialization of our drugs, producing additional losses and depriving us of potential revenue. Although we believe that there are several potential alternative third parties who could store and distribute drug supplies for our clinical trials, we may incur added costs and delays in identifying and qualifying any such replacement.

Our arginase inhibitors program in hematology and oncology indications, including CB-1158, is reliant in part on Incyte for the successful development and commercialization in a timely manner. If Incyte does not devote sufficient resources to CB-1158's development, is unsuccessful in its efforts, or chooses to terminate its agreement with us, our business, operating results and financial condition will be harmed.

We have entered into a collaboration agreement with Incyte under which we have granted Incyte an exclusive, worldwide license to develop and commercialize small molecule arginase inhibitors for hematology and oncology indications, including CB-1158, which is currently in phase 1 clinical trials.

Under the agreement, we and Incyte will jointly conduct and co-fund development of CB-1158, with Incyte leading global development activities. Unless we opt out of our co-funding obligation, Incyte will fund 70 percent of global development and we will be responsible for the remaining 30 percent. Should we disagree with Incyte about the clinical development or commercialization strategy, we could escalate the disagreement to our representatives on the Joint Steering Committee for resolution. Calithera and Incyte are obligated to use good faith efforts to resolve such disputes; however, in cases of deadlock, Incyte will have the deciding vote . If the agreement is terminated, other than as a result of our breach, with respect to one or more products or countries, all rights in the terminated products and countries revert to us The Incyte collaboration may not be clinically or commercially successful due to a number of important factors, including the following:

Subject to the terms of our collaboration agreement, including diligence obligations, although Incyte has certain obligations to use commercially reasonable efforts to develop and commercialize CB-1158, Incyte has discretion in determining the efforts and resources that it will apply to its partnership with us. The timing and amount of any development milestones, and downstream commercial milestones and royalties that we may receive under such

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partnership will depend on, among other things, the efforts, allocation of resources and successful development and commercialization of CB-1158;

• Incyte may select a dose for CB-1158 that does not have a favorable benefit/risk profile;

• Incyte may terminate its partnership with us without cause and for circumstances outside of our control, which could make it difficult for us to attract new strategic partners or adversely affect how we are perceived in scientific and financial communities;

• Incyte may develop or commercialize CB-1158 in a way that exposes us to potential litigation that could jeopardize or invalidate our intellectual property rights or expose us to potential liability; and

If Incyte were to breach our collaboration agreement, we may need to enforce our rights under the agreement, which could be costly. If we were to terminate our agreement with Incyte due to Incyte's breach or if Incyte were to terminate the agreement without cause, there could be a delay in the return of our rights to CB-1158 and the development and commercialization of CB-1158 would be delayed, curtailed or terminated because we may not have sufficient financial resources or capabilities to continue development and commercialization on our own.

Incyte may enter into one or more transactions with third parties, including a merger, consolidation, reorganization, sale of substantial assets, sale of substantial stock or other change in control, which could divert the attention of its management and adversely affect Incyte's ability to retain and motivate key personnel who are important to the continued development of the small molecule arginase inhibitor program. In addition, the third party to any such transaction could reprioritize Incyte's development programs which could delay the development of our programs or cause Incyte to terminate the agreement.

We have in the past and may seek in the future to selectively establish collaborations, and, if we are unable to establish them on commercially reasonable terms, we may have to alter our development and commercialization plans.

Our drug development programs and the potential commercialization of our product candidates will require substantial additional cash to fund expenses. In addition to our collaboration with Incyte, for some of our product candidates, we may decide to collaborate with additional pharmaceutical and biotechnology companies for the development and potential commercialization of those product candidates.

We may also be restricted under existing license agreements from engaging in research and development activities or entering into future agreements on certain terms with potential collaborators. For example, pursuant to our license agreement with Symbioscience, we have agreed not to develop any other arginase inhibitors for use in human healthcare outside of the scope of that agreement. In addition, under our agreement with Incyte, we are not allowed to develop any retained arginase inhibitors (small molecule arginase inhibitors, other than CB-1158, retained by Calithera for research and development in non-hematology/ oncology indications) for any indication except specific orphan indications outside of hematology and oncology.

We face significant competition in seeking appropriate collaborators. Whether we reach a definitive agreement for a collaboration will depend, among other things, upon our assessment of the collaborator's resources and expertise, the terms and conditions of the proposed collaboration and the proposed collaborator's evaluation of a number of factors. Those factors may include the design or results of clinical trials, the likelihood of approval by the FDA or similar regulatory authorities outside the United States, the potential market for the subject product candidate, the costs and complexities of manufacturing and delivering such product candidate to patients, the potential of competing products, the existence of uncertainty with respect to our ownership of technology, which can exist if there is a challenge to such ownership without regard to the merits of the challenge and industry and market conditions generally. The collaborator may also consider alternative product candidates for similar indications that may be available to collaborate on and whether such a collaboration could be more attractive than the one with us for our product candidate.

Collaborations are complex and time-consuming to negotiate and document. In addition, there have been a significant number of recent business combinations among large pharmaceutical companies that have resulted in a reduced number of potential future collaborators.

If we decide to collaborate with any other third parties in connection with any of our development programs or product candidates, we may not be able to negotiate collaborations on a timely basis, on acceptable terms, or at all. If we are unable to do so, we may have to curtail the development program or the product candidate for which we are seeking to collaborate, reduce or delay its development program or one or more of our other development programs, delay its potential commercialization or reduce the scope of any sales or marketing activities, or increase our expenditures and undertake development or commercialization activities at our own expense. If we elect to increase our expenditures to fund development or commercialization activities on our own, we may need to obtain additional capital, which may not be available to us on acceptable terms or at all. If we do not have sufficient funds, we may not be able to further develop our product candidates or bring them to market and generate product revenue.

To the extent we enter into any other collaborations, we may depend on such collaborations for the development and commercialization of our product candidates. If those collaborations are not successful, we may not be able to capitalize on the market potential of our product candidates.

We may selectively seek additional third-party collaborators for the development and commercialization of our product candidates. Our current and any future collaborators for any collaboration arrangements include large and mid-size pharmaceutical companies, regional and national pharmaceutical companies and biotechnology companies. Pursuant to these arrangements and any potential future arrangements, we will have limited control over the amount and timing of resources that our collaborators dedicate to the development or commercialization of our product candidates. Our ability to generate revenue from these arrangements will depend on our collaborators' abilities to successfully perform the functions assigned to them in these arrangements.

Collaborations involving our product candidates, including our collaboration with Incyte, pose many risks to us, including that:

- Collaborators have significant discretion in determining the efforts and resources that they will apply to these collaborations.
- Collaborators may not pursue development and commercialization of our product candidates or may elect not to continue or renew development or commercialization programs based on clinical trial results, changes in the collaborator's strategic focus or available funding or external factors such as an acquisition that diverts resources or creates competing priorities.
- Collaborators may delay clinical trials, provide insufficient funding for a clinical trial program, stop a clinical trial or abandon a product candidate, repeat or conduct new clinical trials or require a new formulation of a product candidate for clinical testing.
- Collaborators could independently develop, or develop with third parties, products that compete directly or indirectly with our product candidates or products if the collaborators believe that competitive products are more likely to be successfully developed or can be commercialized under terms that are more economically attractive than ours.
- A collaborator with marketing and distribution rights to one or more product candidates or products may not commit sufficient resources to the marketing and distribution of such drugs.
- Collaborators may not properly maintain or defend our intellectual property rights or may use our proprietary information in such a way as to invite litigation that could jeopardize or invalidate our proprietary information or expose us to potential litigation.
- Disputes may arise between the collaborators and us that result in the delay or termination of the research, development or commercialization of our product candidates or products or that result in costly litigation or arbitration that diverts management attention and resources.
- We may lose certain valuable rights under circumstances identified in our collaborations if we undergo a change of control.
- Collaborations may be terminated and, if terminated, may result in a need for additional capital to pursue further development or commercialization of the applicable product candidates.
 - Collaboration agreements may not lead to development or commercialization of product candidates in the most efficient manner or at all. If a future collaborator of ours were to be involved in a business combination, the continued pursuit and emphasis on our product development or commercialization program under such collaboration could be delayed, diminished or terminated.

We have in-licensed portfolios of arginase inhibitors and hexokinase II inhibitors, respectively, as part of our efforts to develop product candidates for these programs, and we are substantially dependent on these in-licenses for these programs. To the extent these in-licenses are terminated, our business may be harmed.

Risks Related to Our Intellectual Property

Recent laws and rulings by U.S. courts make it difficult to predict how patents will be issued or enforced in our industry.

Changes in either the patent laws or interpretation of the patent laws in the United States and other countries may have a significant impact on our ability to protect our technology and enforce our intellectual property rights. There have been numerous recent changes to the patent laws and to the rules of the United States Patent and Trademark Office, or the USPTO, which may have a significant impact on our ability to protect our technology and enforce our intellectual property rights. For example, the Leahy-Smith America Invents Act, which was signed into law in 2011, includes a transition from a “first-to-invent” system to a “first-to-file” system, and changes the way issued patents are challenged. Certain changes, such as the institution of inter partes review proceedings,

came into effect on September 16, 2012. Substantive changes to patent law associated with the America Invents Act may affect our ability to obtain patents, and, if obtained, to enforce or defend them in litigation or post-grant proceedings, all of which could harm our business.

Furthermore, the patent positions of companies engaged in the development and commercialization of biologics and pharmaceuticals are particularly uncertain. Two cases involving diagnostic method claims and “gene patents” have recently been decided by the Supreme Court. On March 20, 2012, the Supreme Court issued a decision in *Mayo Collaborative Services v. Prometheus Laboratories, Inc.*, or *Prometheus*, a case involving patent claims directed to measuring a metabolic product in a patient to optimize a drug dosage amount for the patient. According to the Supreme Court, the addition of well-understood, routine or conventional activity such as “administering” or “determining” steps was not enough to transform an otherwise patent ineligible natural phenomenon into patent eligible subject matter. On July 3, 2012, the USPTO issued guidance indicating that process claims directed to a law of nature, a natural phenomenon or an abstract idea that do not include additional elements or steps that integrate the natural principle into the claimed invention such that the natural principle is practically applied and the claim amounts to significantly more than the natural principle itself should be rejected as directed to non-statutory subject matter. On June 13, 2013, the Supreme Court issued its decision in *Association for Molecular Pathology v. Myriad Genetics, Inc.*, or *Myriad*, a case involving patent claims held by Myriad Genetics, Inc. relating to the breast cancer susceptibility genes BRCA1 and BRCA2. Myriad held that isolated segments of naturally occurring DNA, such as the DNA constituting the BRCA1 and BRCA2 genes, is not patent eligible subject matter, but that complementary DNA, which is an artificial construct that may be created from RNA transcripts of genes, may be patent eligible.

We cannot assure you that our efforts to seek patent protection for our technology and products will not be negatively impacted by the decisions described above, rulings in other cases or changes in guidance or procedures issued by the USPTO. We cannot fully predict what impact the Supreme Court’s decisions in *Prometheus* and *Myriad* may have on the ability of life science companies to obtain or enforce patents relating to their products and technologies in the future.

Moreover, although the Supreme Court has held in *Myriad* that isolated segments of naturally occurring DNA are not patent-eligible subject matter, certain third parties could allege that activities that we may undertake infringe other gene-related patent claims, and we may deem it necessary to defend ourselves against these claims by asserting non-infringement and/or invalidity positions, or pay to obtain a license to these claims. In any of the foregoing or in other situations involving third-party intellectual property rights, if we are unsuccessful in defending against claims of patent infringement, we could be forced to pay damages or be subjected to an injunction that would prevent us from utilizing the patented subject matter. Such outcomes could harm our business.

If we are alleged to infringe intellectual property rights of third parties, our business could be harmed.

Our research, development and commercialization activities may be alleged to infringe patents, trademarks or other intellectual property rights owned by other parties. Certain of our competitors and other companies in the industry have substantial patent portfolios and may attempt to use patent litigation as a means to obtain a competitive advantage. We may be a target for such litigation. Even if our pending patent applications issue, they may relate to our competitors’ activities and may therefore not deter litigation against us. The risks of being involved in such litigation may also increase as we become more visible as a public company and move into new markets and applications for our product candidates. There may also be patents and patent applications that are relevant to our technologies or product candidates that are unknown to us. For example, certain relevant patent applications may have been filed but not published. If such patents exist, or if a patent issues on any of such patent applications, that patent could be asserted against us. Third parties could bring claims against us that would cause us to incur substantial expenses and, if the claims against us are successful, could cause us to pay substantial damages, including treble damages and attorneys’ fees for willful infringement. The defense of such a suit could also divert the attention of our management

and technical personnel. Further, if an intellectual property infringement suit were brought against us, we could be forced to stop or delay research, development or sales of the product that is the subject of the suit.

As a result of infringement claims, or to avoid potential claims, we may choose or be compelled to seek intellectual property licenses from third parties. These licenses may not be available on acceptable terms, or at all. Even if we are able to obtain a license, the license would likely obligate us to pay license fees or royalties or both, and the rights granted to us likely would be nonexclusive, which would mean that our competitors also could obtain licenses to the same intellectual property. Ultimately, we could be prevented from commercializing a product candidate and/or technology or be forced to cease some aspect of our business operations if, as a result of actual or threatened infringement claims, we are unable to enter into licenses of the relevant intellectual property on acceptable terms. Further, if we attempt to modify a product candidate and/or technology or to develop alternative methods or products in response to infringement claims or to avoid potential claims, we could incur substantial costs, encounter delays in product introductions or interruptions in sales.

We may become involved in other lawsuits to protect or enforce our patents or other intellectual property, which could be expensive and time-consuming, and an unfavorable outcome could harm our business.

In addition to the possibility of litigation relating to infringement claims asserted against us, we may become a party to other patent litigation and other proceedings, including inter partes review proceedings, post-grant review proceedings, derivation proceedings declared by the USPTO and similar proceedings in foreign countries, regarding intellectual property rights with respect to our current or future technologies or product candidates or products. The cost to us of any patent litigation or other proceeding, even if resolved in our favor, could be substantial. Some of our competitors may be able to sustain the costs of such litigation or proceedings more effectively than we can because of their substantially greater financial resources. Patent litigation and other proceedings may also absorb significant management time. Uncertainties resulting from the initiation and continuation of patent litigation or other proceedings could impair our ability to compete in the marketplace.

Competitors may infringe or otherwise violate our intellectual property, including patents that may issue to or be licensed by us. As a result, we may be required to file claims in an effort to stop third-party infringement or unauthorized use. Any such claims could provoke these parties to assert counterclaims against us, including claims alleging that we infringe their patents or other intellectual property rights. This can be expensive, particularly for a company of our size, and time-consuming, and even if we are successful, any award of monetary damages or other remedy we may receive may not be commercially valuable. In addition, in an infringement proceeding, a court may decide that our asserted intellectual property is not valid or is unenforceable, or may refuse to stop the other party from using the technology at issue on the grounds that our intellectual property does not cover its technology. An adverse determination in any litigation or defense proceedings could put our intellectual property at risk of being invalidated or interpreted narrowly and could put our patent applications at risk of not issuing.

If the breadth or strength of our patent or other intellectual property rights is compromised or threatened, it could allow third parties to commercialize our technology or products or result in our inability to commercialize our technology and products without infringing third-party intellectual property rights. Further, third parties may be dissuaded from collaborating with us.

Interference or derivation proceedings brought by the USPTO or its foreign counterparts may be necessary to determine the priority of inventions with respect to our patent applications, and we may also become involved in other proceedings, such as re-examination proceedings, before the USPTO or its foreign counterparts. Due to the substantial competition in the pharmaceutical space, the number of such proceedings may increase. This could delay the prosecution of our pending patent applications or impact the validity and enforceability of any future patents that we may obtain. In addition, any such litigation, submission or proceeding may be resolved adversely to us and, even if successful, may result in substantial costs and distraction to our management.

Furthermore, because of the substantial amount of discovery required in connection with intellectual property litigation, there is a risk that some of our confidential information could be compromised by disclosure during this type of litigation. Moreover, intellectual property law relating to the fields in which we operate is still evolving and, consequently, patent and other intellectual property positions in our industry are subject to change and are often uncertain. We may not prevail in any of these suits or other efforts to protect our technology, and the damages or other remedies awarded, if any, may not be commercially valuable. During the course of this type of litigation, there could be public announcements of the results of hearings, motions or other interim proceedings or developments. If securities analysts or investors perceive these results to be negative, the market price for our common stock could be significantly harmed.

We may not be able to protect our intellectual property rights throughout the world, which could impair our competitive position.

Filing, prosecuting, defending and enforcing patents on all of our technologies, product candidates and products throughout the world would be prohibitively expensive. As a result, we seek to protect our proprietary position by filing patent applications in the United States and in select foreign jurisdictions and cannot guarantee that we will obtain the patent protection necessary to protect our competitive position in all major markets. Competitors may use our technologies in jurisdictions where we have not obtained patent protection to develop their own products and, further, may export infringing products to territories where we may obtain patent protection but where enforcement is not as strong as that in the United States. These products may compete with our current and future products in jurisdictions where we do not have any issued patents, and our patent claims or other intellectual property rights may not be effective or sufficient to prevent them from so competing.

Many companies have encountered significant problems in protecting and defending intellectual property rights in foreign jurisdictions. The legal systems of certain countries, particularly certain developing countries, do not favor the enforcement of patents and other intellectual property protection, which could make it difficult for us to stop the infringement of our patents or the marketing of competing products in violation of our proprietary rights generally. The legal systems of certain countries make it difficult or impossible to obtain patent protection for pharmaceutical products and services. Proceedings to enforce our patent rights in foreign jurisdictions could result in substantial costs and could divert our efforts and attention from other aspects of our business.

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

In addition to seeking patents for some of our technologies and product candidates, we also rely on trade secrets, including unpatented know-how, technology and other proprietary information, to maintain our competitive position. We seek to protect these trade secrets, in part, by entering into non-disclosure and confidentiality agreements with parties who have access to them, such as our employees, corporate collaborators, outside scientific collaborators, contract manufacturers, consultants, advisors and other third parties. We also enter into confidentiality and invention assignment agreements with our employees and consultants that obligate them to assign to us any inventions developed in the course of their work for us. However, we cannot guarantee that we have executed these agreements with each party that may have or have had access to our trade secrets or that the agreements we have executed will provide adequate protection. Despite these efforts, any of these parties may breach the agreements and disclose our proprietary information, including our trade secrets, and we may not be able to obtain adequate remedies for such breaches. As a result, we may be forced to bring claims against third parties, or defend claims that they bring against us, to determine ownership of what we regard as our intellectual property. Monitoring unauthorized disclosure is difficult and we do not know whether the procedures we have followed to prevent such disclosure are, or will be adequate. Enforcing a claim that a party illegally disclosed or misappropriated a trade secret is difficult, expensive and time-consuming, and the outcome is unpredictable. In addition, some courts inside and outside the United States may be less willing or unwilling to protect trade secrets. If any of the technology or information that we protect as trade secrets were to be lawfully obtained or independently developed by a competitor, we would have no right to prevent them from using that technology or information to compete with us. If any of our trade secrets were to be disclosed to, or independently developed by, a competitor, our competitive position would be harmed.

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

Our trademarks or trade names may be challenged, infringed, circumvented, declared generic or determined to be infringing on other marks. As a means to enforce our trademark rights and prevent infringement, we may be required to file trademark claims against third parties or initiate trademark opposition proceedings. This can be expensive and time-consuming, particularly for a company of our size. In addition, in an infringement proceeding, a court may decide that a trademark of ours is not valid or is unenforceable, or may refuse to stop the other party from using the trademark at issue. We may not be able to protect our rights to these and other trademarks and trade names which we need to build name recognition by potential partners or customers in our markets of interest. We do not currently have any registered trademarks in the United States. Any trademark applications in the United States and in other foreign jurisdictions where we may file may not be allowed or may subsequently be opposed. In addition, other companies in the biopharmaceutical space may be using trademarks that are similar to ours and may in the future allege that our use of the trademark infringes or otherwise violates their trademarks. Over the long term, if we are unable to establish name recognition based on our trademarks and trade names, then we may not be able to compete effectively and our business may be harmed.

Third parties may assert ownership or commercial rights to inventions we develop.

Third parties may in the future make claims challenging the inventorship or ownership of our intellectual property. We have written agreements with collaborators that provide for the ownership of intellectual property arising from our collaborations. In some instances, there may not be adequate written provisions to address clearly the resolution of intellectual property rights that may arise from a collaboration. If we cannot successfully negotiate sufficient ownership and commercial rights to the inventions that result from our collaborations, or if disputes otherwise arise with respect to the intellectual property developed in the course of a collaboration, we may be limited in our ability to capitalize on the market potential of these inventions.

In addition, we may face claims by third parties that our agreements with employees, contractors or consultants obligating them to assign intellectual property to us are ineffective or are in conflict with prior or competing contractual obligations of assignment, which could result in ownership disputes regarding intellectual property we have developed or will develop and interfere with our ability to capture the commercial value of such inventions. Litigation may be necessary to resolve an ownership dispute, and if we are not successful, we may be precluded from using certain intellectual property, or may lose our exclusive rights in that intellectual property. Either outcome could have an adverse impact on our business.

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

Even if we complete the necessary preclinical studies and clinical trials, the marketing approval process is expensive, time-consuming and uncertain and may prevent us from obtaining approvals for the commercialization of some or all of our product candidates. If we or our collaborators are not able to obtain, or if there are delays in obtaining, required regulatory approvals, we will not be able to commercialize, or will be delayed in commercializing, our product candidates, and our ability to generate revenue will be impaired.

Our product candidates and the activities associated with their development and commercialization, including their design, testing, manufacture, safety, efficacy, recordkeeping, labeling, storage, approval, advertising, promotion, sale and distribution, are subject to comprehensive regulation by the FDA and other regulatory agencies in the United States and by comparable authorities in other countries. Failure to obtain marketing approval for a product candidate will prevent us from commercializing the product candidate. We have not received approval to market any of our product candidates from regulatory authorities in any jurisdiction. We have only limited experience in filing and supporting the applications necessary to gain marketing approvals and expect to rely on third-party contract research organizations to assist us in this process. Securing regulatory approval requires the submission of extensive preclinical and clinical data and supporting information to the various regulatory authorities for each therapeutic indication to establish the product candidate's safety and efficacy. Securing regulatory approval also requires the submission of information about the product manufacturing process to, and inspection of manufacturing facilities by, the relevant regulatory authority. Our product candidates may not be effective, may be only moderately effective or may prove to have undesirable or unintended side effects, toxicities or other characteristics that may preclude our obtaining marketing approval or prevent or limit commercial use.

The process of obtaining marketing approvals, both in the United States and elsewhere, is expensive, may take many years and can vary substantially based upon a variety of factors, including the type, complexity and novelty of the product candidates involved. We cannot assure you that we will ever obtain any marketing approvals in any jurisdiction. Changes in marketing approval policies during the development period, changes in or the enactment of additional statutes or regulations or changes in regulatory review for each submitted product application may cause delays in the approval or rejection of an application. The FDA and comparable authorities in other countries have substantial discretion in the approval process and may refuse to accept any application or may decide that our data is insufficient for approval and require additional preclinical or other studies, and clinical trials. In addition, varying interpretations of the data obtained from preclinical testing and clinical trials could delay, limit or prevent marketing approval of a product candidate. Additionally, any marketing approval we ultimately obtain may be limited or subject to restrictions or post-approval commitments that render the approved product not commercially viable.

Any product candidate for which we obtain marketing approval could be subject to marketing restrictions or withdrawal from the market, and we may be subject to penalties if we fail to comply with regulatory requirements or if we experience unanticipated problems with our products.

Any product candidate for which we obtain marketing approval, along with the manufacturing processes, post-approval clinical data, labeling, advertising and promotional activities for such product, will be subject to continual requirements of and review by the FDA and other regulatory authorities. These requirements include submissions of safety and other post-marketing information and reports, registration and listing requirements, cGMP requirements, quality assurance and corresponding maintenance of records and documents and requirements regarding the distribution of samples to physicians and recordkeeping. Even if marketing approval of a product candidate is granted, the approval may be subject to limitations on the indicated uses for which the product may be marketed or to the conditions of approval, or contain requirements for costly post-marketing testing and surveillance to monitor the safety or efficacy of the medicine. The FDA closely regulates the post approval marketing and promotion of drugs to ensure that they are marketed only for the approved indications and in accordance with the provisions of the approved

labeling. The FDA imposes stringent restrictions on manufacturers' communications regarding off-label use and if we do not market our products for their approved indications, we may be subject to enforcement action for off-label marketing.

In addition, later discovery of previously unknown problems with our products, manufacturers or manufacturing processes, or failure to comply with regulatory requirements, may result in, among other things:

- restrictions on such products, manufacturers or manufacturing processes;
- restrictions on the labeling, marketing, distribution or use of a product;
- requirements to conduct post-approval clinical trials;
- warning or untitled letters;
- withdrawal of the products from the market;
- refusal to approve pending applications or supplements to approved applications that we submit;

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- recall of products;
- fines, restitution or disgorgement of profits or revenue;
- suspension or withdrawal of marketing approvals;
- refusal to permit the import or export of our products;
- product seizure; and
- injunctions or the imposition of civil or criminal penalties.

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

Healthcare providers, physicians and third-party payors play a primary role in the recommendation and prescription of any product candidates for which we obtain marketing approval. Our future arrangements with third-party payors and customers may expose us to broadly applicable fraud and abuse and other healthcare laws and regulations that may constrain the business or financial arrangements and relationships through which we market, sell and distribute our medicines for which we obtain marketing approval. Restrictions under applicable federal and state healthcare laws and regulations include the following:

- the federal healthcare anti-kickback statute prohibits, among other things, persons from knowingly and willfully soliciting, offering, receiving or providing remuneration, directly or indirectly, in cash or in kind, to induce or reward either the referral of an individual for, or the purchase, order or recommendation of, any good or service, for which payment may be made under federal and state healthcare programs such as Medicare and Medicaid;
- the federal False Claims Act imposes criminal and civil penalties, including civil whistleblower or qui tam actions, against individuals or entities for knowingly presenting, or causing to be presented, to the federal government, claims for payment that are false or fraudulent or making a false statement to avoid, decrease or conceal an obligation to pay money to the federal government;
- the federal Health Insurance Portability and Accountability Act of 1996, as amended by the Health Information Technology for Economic and Clinical Health Act, imposes criminal and civil liability for executing a scheme to defraud any healthcare benefit program and also imposes obligations, including mandatory contractual terms, with respect to safeguarding the privacy, security and transmission of individually identifiable health information;
- the federal false statements statute prohibits knowingly and willfully falsifying, concealing or covering up a material fact or making any materially false statement in connection with the delivery of or payment for healthcare benefits, items or services;
- the Physician Payments Sunshine Act requires manufacturers of drugs, devices, biologics and medical supplies to report to the Department of Health and Human Services information related to physician payments and other transfers of value and physician ownership and investment interests; and
- analogous state laws and regulations, such as state anti-kickback and false claims laws, may apply to sales or marketing arrangements and claims involving healthcare items or services reimbursed by non-governmental third-party payors, including private insurers, and some state laws require pharmaceutical companies to comply with the pharmaceutical industry's voluntary compliance guidelines and the relevant compliance guidance promulgated by the federal government in addition to requiring drug manufacturers to report information related to payments to physicians and other health care providers or marketing expenditures.

Efforts to ensure that our business arrangements with third parties will comply with applicable healthcare laws and regulations will involve substantial costs. It is possible that governmental authorities will conclude that our business practices may not comply with current or future statutes, regulations or case law involving applicable fraud and abuse or other healthcare laws and regulations. If our operations are found to be in violation of any of these laws or any other governmental regulations that may apply to us, we may be subject to significant civil, criminal and administrative penalties, damages, fines, exclusion from government funded healthcare programs, such as Medicare and Medicaid, and the curtailment or restructuring of our operations. If any of the physicians or other providers or entities with whom we expect to do business are found to be not in compliance with applicable laws, they may be

subject to criminal, civil or administrative sanctions, including exclusions from government funded healthcare programs.

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Recently enacted and future legislation may increase the difficulty and cost for us to obtain marketing approval of and commercialize our product candidates and affect the prices we may obtain.

In the United States and some foreign jurisdictions, there have been a number of legislative and regulatory changes and proposed changes regarding the healthcare system that could prevent or delay marketing approval of our product candidates, restrict or regulate post-approval activities and affect our ability to profitably sell any product candidates for which we obtain marketing approval.

The Medicare Prescription Drug, Improvement, and Modernization Act of 2003, or Medicare Modernization Act, changed the way Medicare covers and pays for pharmaceutical products. The legislation expanded Medicare coverage for drug purchases by the elderly and introduced a new reimbursement methodology based on average sales prices for physician-administered drugs. In addition, this legislation provided authority for limiting the number of drugs that will be covered in any therapeutic class. Cost reduction initiatives and other provisions of this legislation could decrease the coverage and price that we receive for any approved products. While the Medicare Modernization Act applies only to drug benefits for Medicare beneficiaries, private payors often follow Medicare coverage policy and payment limitations in setting their own reimbursement rates. Therefore, any reduction in reimbursement that results from the Medicare Modernization Act may result in a similar reduction in payments from private payors.

We expect that healthcare reform measures that may be adopted in the future, could have a material adverse effect on our industry generally and on our ability to maintain or increase sales of any of our product candidates that we successfully commercialize.

Legislative and regulatory proposals have been made to expand post-approval requirements and restrict sales and promotional activities for pharmaceutical products. We cannot be sure whether additional legislative changes will be enacted, or whether the FDA regulations, guidance or interpretations will be changed, or what the impact of such changes on the marketing approvals of our product candidates, if any, may be. In addition, increased scrutiny by the U.S. Congress of the FDA's approval process may significantly delay or prevent marketing approval, as well as subject us to more stringent product labeling and post-marketing testing and other requirements.

Risks Related to Employee Matters and Managing Growth

Our future success depends on our ability to retain our senior management team and to attract, retain and motivate qualified personnel.

We are highly dependent upon our senior management team, as well as the other principal members of our research and development teams. All of our executive officers are employed "at will," meaning we or they may terminate the employment relationship at any time. We do not maintain "key person" insurance for any of our executives or other employees. The loss of the services of any of these persons could impede the achievement of our research, development and commercialization objectives.

Recruiting and retaining qualified scientific, clinical, manufacturing and sales and marketing personnel will also be critical to our success. We may not be able to attract and retain these personnel on acceptable terms given the competition among numerous pharmaceutical and biotechnology companies for similar personnel. We also experience competition for the hiring of scientific and clinical personnel from universities and research institutions. In addition, we rely on consultants and advisors, including scientific and clinical advisors, to assist us in formulating our research and development and commercialization strategy. Our consultants and advisors may be employed by employers other than us and may have commitments under consulting or advisory contracts with other entities that may limit their availability to us.

We expect to expand our operations, and may encounter difficulties in managing our growth, which could disrupt our business.

We expect to expand the scope of our operations, particularly in the areas of drug development, regulatory affairs and sales and marketing. To manage our anticipated future growth, we must continue to implement and improve our managerial, operational and financial systems, expand our facilities and continue to recruit and train additional qualified personnel. We may not be able to effectively manage the expected expansion of our operations or recruit and train additional qualified personnel. Moreover, the expected expansion of our operations may lead to significant costs and may divert our management and business development resources. For example, our facilities expenses may increase, or decrease which will vary depending on the time and terms of any facility lease or sublease we may enter into from time to time. Any inability to manage growth could delay the execution of our business plans or disrupt our operations.

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

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

Risks Related to Our Common Stock

The trading price of our common stock is likely to be volatile, and purchasers of our common stock could incur substantial losses.

Our stock price has fluctuated in the past and is likely to be volatile in the future. The stock market in general and the market for biotechnology companies in particular have experienced extreme volatility that has often been unrelated to the operating performance of particular companies. As a result of this volatility, investors may experience losses on their investment in our common stock. The market price for our common stock may be influenced by many factors, including:

- the success of competitive products or technologies;
 - regulatory actions with respect to our product candidates or our competitors' product and product candidates;
- announcements by us or our competitors of significant acquisitions, strategic partnerships, joint ventures, collaborations or capital commitments;
- results of clinical trials of our product candidates or those of our competitors;
- regulatory or legal developments in the United States and other countries;
- developments or disputes concerning patent applications, issued patents or other proprietary rights;
- the recruitment or departure of key personnel;
- actual and anticipated fluctuations in our quarterly operating results;
- the level of expenses related to any of our product candidates or clinical development programs;
- the results of our efforts to in-license or acquire additional products or product candidates;
- actual or anticipated changes in estimates as to financial results, development timelines or recommendations by securities analysts;
- variations in our financial results or those of companies that are perceived to be similar to us;
- fluctuations in the valuation of companies perceived by investors to be comparable to us;
- inconsistent trading volume levels of our shares;
- announcement or expectation of additional financing efforts;
- sales of our common stock by us, our insiders or our other stockholders;
- changes in the structure of healthcare payment systems;
- market conditions in the pharmaceutical and biotechnology sectors;
- general economic, industry and market conditions; and

the other factors described in this “Risk Factors” section.

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In addition, in the past, stockholders have initiated class action lawsuits against companies following periods of volatility in the market prices of these companies' stock. Such litigation, if instituted against us, could cause us to incur substantial costs and divert management's attention and resources.

Concentration of ownership of our common stock among our existing executive officers, directors and principal stockholders may prevent new investors from influencing significant corporate decisions.

Our executive officers, directors and current beneficial owners of 5% or more of our common stock, in the aggregate, beneficially own a significant percentage of our outstanding common stock. These persons, acting together, will be able to significantly influence all matters requiring stockholder approval, including the election and removal of directors and any merger or other significant corporate transactions. The interests of this group of stockholders may not coincide with the interests of other stockholders.

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

The trading market for our common stock will depend in part on the research and reports that securities or industry analysts publish about us or our business, our market and our competitors. We do not have any control over these analysts. If one or more of the analysts who cover us downgrade our shares or change their opinion of our shares, our share price would likely decline. If one or more of these analysts cease coverage of our company or fail to regularly publish reports on us, we could lose visibility in the financial markets, which could cause our share price or trading volume to decline.

We will incur costs and demands upon management as a result of complying with the laws and regulations affecting public companies in the United States, which may harm our operating results.

As a public company listed in the United States, we have and will continue to incur significant additional legal, accounting and other expenses. In addition, changing laws, regulations and standards relating to corporate governance and public disclosure, including regulations implemented by the Securities and Exchange Commission, or the SEC, and the NASDAQ Global Select Market, may increase legal and financial compliance costs and make some activities more time-consuming. These laws, regulations and standards are subject to varying interpretations, and as a result, their application in practice may evolve over time as new guidance is provided by regulatory and governing bodies. We intend to invest resources to comply with evolving laws, regulations and standards, and this investment may result in increased general and administrative expenses and a diversion of management's time and attention from revenue-generating activities to compliance activities. If, notwithstanding our efforts to comply with new laws, regulations and standards, we fail to comply, regulatory authorities may initiate legal proceedings against us, and our business may be harmed.

Further, failure to comply with these laws, regulations and standards might also make it more difficult for us to obtain certain types of insurance, including director and officer liability insurance, and we might be forced to accept reduced policy limits and coverage or incur substantially higher costs to obtain the same or similar coverage. The impact of these events could also make it more difficult for us to attract and retain qualified persons to serve on our Board of Directors, on committees of our Board of Directors or as members of senior management.

We do not anticipate paying any cash dividends on our common stock so any returns will be limited to changes in the value of our common stock.

We have never declared or paid cash dividends on our common stock. We currently intend to retain our future earnings, if any, to fund the development and growth of our business. In addition, the terms of any existing or future

credit facility may restrict our ability to pay dividends. Any return to stockholders will therefore be limited to the increase, if any, of our stock price.

We are an “emerging growth company,” and we expect to comply with the reduced disclosure requirements applicable to emerging growth companies, which could make our common stock less attractive to investors.

We are an “emerging growth company,” as defined in the Jumpstart Our Business Startups Act, or JOBS Act, enacted in April 2012, and for as long as we continue to be an “emerging growth company,” we expect to take advantage of exemptions from various reporting requirements applicable to other public companies but not to “emerging growth companies,” including, but not limited to, not being required to comply with the auditor attestation requirements of Section 404, reduced disclosure obligations regarding executive compensation in our periodic reports and proxy statements and exemptions from the requirements of holding a nonbinding advisory vote on executive compensation and shareholder approval of any golden parachute payments not previously approved. We will continue to be an “emerging growth company” until the earlier of (1) the last day of the fiscal year (a) following the fifth

anniversary of the closing of our initial public offering in October 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 exceeds \$700 million as of the prior June 30, and (2) the date on which we have issued more than \$1.0 billion in non-convertible debt during the prior three-year period. We cannot predict if investors will find our common stock less attractive by our reliance on these exemptions. If some investors find our common stock less attractive as a result of our choices to reduce disclosure, there may be a less active trading market for our common stock, and our stock price may be more volatile.

If we are unable to maintain proper and effective internal controls over financial reporting, the accuracy and timeliness of our financial reporting may be adversely affected.

Effective internal controls are necessary for us to provide reliable financial reports and to protect from fraudulent, illegal or unauthorized transactions. If we cannot provide effective controls and reliable financial reports, our business and operating results could be harmed. We have in the past discovered, and may in the future discover, areas of our internal controls that need improvement. We are required, pursuant to Section 404 of the Sarbanes-Oxley Act, to furnish a report by management on the effectiveness of our internal control over financial reporting as of December 31, 2016. Our independent registered public accounting firm will not be required to attest to the effectiveness of our internal control over financial reporting until our first annual report required to be filed with the SEC following the later of the date we are deemed to be a “large accelerated filer,” each as defined in the Exchange Act, or the date we are no longer an “emerging growth company,” as defined in the JOBS Act.

If material weaknesses or control deficiencies occur in the future, we may be unable to report our financial results accurately on a timely basis, which could cause our reported financial results to be materially misstated and result in the loss of investor confidence and cause the market price of our common stock to decline.

Provisions in our corporate charter documents and under Delaware law may prevent or frustrate attempts by our stockholders to change our management or hinder efforts to acquire a controlling interest in us, and the market price of our common stock may be lower as a result.

There are provisions in our certificate of incorporation and bylaws that may make it difficult for a third party to acquire, or attempt to acquire, control of our company, even if a change in control was considered favorable by our stockholders.

Our charter documents also contain other provisions that could have an anti-takeover effect, such as:

- establishing a classified Board of Directors so that not all members of our Board of Directors are elected at one time;
- permitting the Board of Directors to establish the number of directors and fill any vacancies and newly created directorships;
- providing that directors may only be removed for cause;
- prohibits cumulative voting for directors;
- requiring super-majority voting to amend some provisions in our certificate of incorporation and bylaws;
- authorizing the issuance of “blank check” preferred stock that our Board of Directors could use to implement a stockholder rights plan;
- eliminating the ability of stockholders to call special meetings of stockholders; and
- prohibiting stockholder action by written consent, which requires all stockholder actions to be taken at a meeting of our stockholders.

Moreover, because we are incorporated in Delaware, we are governed by the provisions of Section 203 of the Delaware General Corporation Law, which prohibit a person who owns 15% or more of our outstanding voting stock from merging or combining with us for a period of three years after the date of the transaction in which the person

acquired in excess of 15% of our outstanding voting stock, unless the merger or combination is approved in a prescribed manner. Any provision in our certificate of incorporation or our bylaws or Delaware law that has the effect of delaying or deterring a change in control could limit the opportunity for our stockholders to receive a premium for their shares of our common stock, and could also affect the price that some investors are willing to pay for our common stock.

Our amended and restated certificate of incorporation provides that the Court of Chancery of the State of Delaware is the exclusive forum for substantially all disputes between us and our stockholders, which could limit our stockholders' ability to obtain a favorable judicial forum for disputes with us or our directors, officers or employees.

Our amended and restated certificate of incorporation provides that the Court of Chancery of the State of Delaware is the exclusive forum for any derivative action or proceeding brought on our behalf; any action asserting a breach of fiduciary duty; any action asserting a claim against us arising pursuant to the Delaware General Corporation Law, our amended and restated certificate of incorporation or our bylaws; or any action asserting a claim against us that is governed by the internal affairs doctrine. The choice of forum provision may limit a stockholder's ability to bring a claim in a judicial forum that it finds favorable for disputes with us or our directors, officers or other employees, which may discourage such lawsuits against us and our directors, officers and other employees. If a court were to find the choice of forum provision contained in our amended and restated certificate of incorporation to be inapplicable or unenforceable in an action, we may incur additional costs associated with resolving such action in other jurisdictions, which could harm our business and financial condition.

Item 1B. Unresolved Staff Comments.

None.

Item 2. Properties.

Our headquarters are located at 343 Oyster Point Blvd., Suite 200, South San Francisco, California 94080 under a lease that expires in January 2024, with an option to extend another two years to January 2026. We have subleased a portion of this office and laboratory space to another biotechnology company under a three-year sublease agreement that expires in February 2020. We believe that our existing facilities are adequate for our current needs, as the facilities have sufficient laboratory space to house additional employees to be hired as we expand.

Item 3. Legal Proceedings.

From time to time, we may become involved in legal proceedings relating to claims arising from the ordinary course of business. Our management believes that there are currently no claims or actions pending against us, the ultimate disposition of which could have a material adverse effect on our results of operations, financial condition or cash flows.

Item 4. Mine Safety Disclosures.

Not applicable.

PART II

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

Price Range of Common Stock

Our common stock commenced trading on the NASDAQ Global Select Market under the symbol "CALA" on October 2, 2014. Prior to that date, there was no public trading market for our common stock. The following table sets forth, for the periods indicated, the high and low reported sales prices of our common stock as reported on the NASDAQ Global Select Market:

	High	Low
2016		
Fourth Quarter	\$4.25	\$2.20
Third Quarter	\$3.86	\$2.87
2nd Quarter	\$6.16	\$3.60
1st Quarter	\$7.84	\$4.31
2015		
Fourth Quarter	\$10.90	\$5.16
Third Quarter	\$10.59	\$4.31
2nd Quarter	\$19.89	\$6.61
1st Quarter	\$25.41	\$12.31

As of March 10, 2017, there were approximately 30 holders of record of our common stock.

Stock Price Performance Graph

The following stock performance graph compares our total stock return with the total return for (i) the NASDAQ Composite Index and the (ii) the NASDAQ Biotechnology Index for the period from October 2, 2014 (the date our common stock commenced trading on the NASDAQ Select Global Market) through December 31, 2016. The figures represented below assume an investment of \$100 in our common stock at the closing price of \$9.41 on October 2, 2014 and in the NASDAQ Composite Index and the NASDAQ Biotechnology Index on October 2, 2014 and the reinvestment of dividends into shares of common stock. The comparisons in the table are required by the SEC and are not intended to forecast or be indicative of possible future performance of our common stock.

		October	December	December
\$100 investment in stock or index	Ticker	2, 2014	30, 2015	31, 2016
Calithera Biosciences, Inc.	CALA	\$100.00	\$ 81.40	\$ 34.54
NASDAQ Composite Index	IXIC	\$100.00	\$ 113.03	\$ 121.51
NASDAQ Biotechnology Index	NBI	\$100.00	\$ 125.91	\$ 98.61

This graph shall not be deemed “soliciting material” or be deemed “filed” for purposes of Section 18 of the Exchange Act, or otherwise subject to the liabilities under that Section, and shall not be deemed to be incorporated by reference into any of our filings under the Securities Act whether made before or after the date hereof and irrespective of any general incorporation language in any such filing.

Dividend Policy

We have never declared or paid cash dividends on our capital stock. We intend to retain all available funds and any future earnings, if any, to fund the development and expansion of our business and we do not anticipate paying any cash dividends in the foreseeable future. Any future determination related to dividend policy will be made at the discretion of our Board of Directors.

Use of Proceeds from Registered Securities

On October 7, 2014, we closed our initial public offering, or IPO, in which we issued and sold 8,000,000 shares of our common stock at a public offering price of \$10.00 per share, for net proceeds of \$71.6 million, after deducting underwriting discounts and commissions of \$5.6 million and estimated offering expenses of \$2.8 million payable by us. No payments for such expenses were made directly or indirectly to (i) any of our officers or directors or their associates, (ii) any persons owning 10% or more of any class

of our equity securities, or (iii) any of our affiliates. The offer and sale of all of the shares in the IPO were registered under the Securities Act pursuant to a registration statement on Form S-1 (File No. 333-198355), which was declared effective by the SEC on October 1, 2014. Citigroup Global Markets and Leerink Partners acted as joint book-running managers for the offering. Wells Fargo Securities and JMP Securities acted as co-managers for the offering. Following the sale of the shares in connection with the closings of the IPO, the offering terminated.

We have been using and will continue to use the net offering proceeds to advance our product candidates through clinical trial programs and for working capital and general corporate purposes. No such payments were made directly or indirectly by us to directors, officers or persons owning ten percent or more of our common stock.

There has been no material change in the planned use of proceeds from our IPO as described in our prospectus dated October 1, 2014, filed with the SEC pursuant to Rule 424(b) under the Securities Act of 1933, as amended.

Issuer Purchases of Equity Securities

None.

Item 6. Selected Financial Data.

The statements of operations data for the years ended December 31, 2016, 2015, and 2014, and the balance sheet data as of December 31, 2016 and 2015 are derived from our audited financial statements included elsewhere in this Annual Report on Form 10-K. The selected balance sheet data as of December 31, 2014 is derived from our audited financial statements which are not included in this Annual Report on Form 10-K.

Our historical results are not necessarily indicative of the results to be expected in the future. You should read the selected financial data below in conjunction with the section of this report entitled “Item 7. Management’s Discussion and Analysis of Financial Condition and Results of Operations” and our financial statements and the related notes included in this Annual Report on Form 10-K.

	Year Ended December 31,		
	2016	2015	2014
	(in thousands, except per share data)		
Statements of Operation Data:			
Operating expenses:			
Research and development	\$27,748	\$23,748	\$16,367
General and administrative	10,586	9,071	5,354
Total operating expenses	38,334	32,819	21,721
Loss from operations	(38,334)	(32,819)	(21,721)
Interest income	330	175	9
Net loss	\$(38,004)	\$(32,644)	\$(21,712)
Net loss per share, basic and diluted	\$(1.95)	\$(1.81)	\$(4.67)
Shares used in computing net loss per share, basic and diluted	19,486	18,045	4,652

	Year Ended December 31,		
	2016	2015	2014
	(in thousands)		
Balance Sheet Data:			
Cash, cash equivalents, and investments	\$51,781	\$71,925	\$101,969
Working capital	49,108	68,662	99,742
Total assets	54,796	75,750	104,770
Convertible preferred stock	—	—	—
Accumulated deficit	(122,502)	(84,498)	(51,854)
Total stockholders' equity	49,906	71,788	100,366

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

Some of the statements in this "Management's Discussion and Analysis of Financial Condition and Results of Operations" are forward-looking statements. These forward-looking statements are based on management's beliefs and assumptions and on information currently available to our management and involve significant elements of subjective judgment and analysis. Words such as "may," "will," "should," "could," "would," "expect," "plan," "anticipate," "believe," "estimate," "project," "predict," "potential," "seek," "target," "goals," "intend," variations of such words, and similar expressions are intended to identify forward-looking statements. Our actual results and the timing of events may differ significantly from the results discussed in the forward-looking statements. Factors that might cause such a difference include those discussed under the caption "Special Note Regarding Forward Looking Statements" and in "Risk Factors" and elsewhere in this Annual Report on Form 10-K. These and many other factors could affect our future financial and operating results. We undertake no obligation to update any forward-looking statement to reflect events after the date of this Annual Report on Form 10-K.

Overview

We are a clinical-stage pharmaceutical company focused on discovering and developing novel small molecule oncology drugs directed against tumor and immune cell targets that control key metabolic pathways in the tumor microenvironment. Tumor metabolism and immuno-oncology have emerged as promising new fields for cancer drug discovery, and recent clinical successes with therapeutic agents in each field have demonstrated the potential to create fundamentally new therapies for cancer patients. We are developing agents that take advantage of the unique metabolic requirements of tumor cells and cancer-fighting immune cells such as cytotoxic T-cells. Our lead product candidate, CB-839, is an internally discovered, first-in-class oral inhibitor of glutaminase, a critical enzyme in tumor cells. We are currently evaluating CB-839 in multiple Phase 1b clinical trials in solid tumors. CB-839 administered as a single agent has resulted in clinical responses in renal cell cancer and acute myeloid leukemia and clinical benefit in several other tumor types. We are currently enrolling patients in a series of combination Phase 1b cohorts in specific solid tumor types, and are planning to begin Phase 2 trials in renal cell carcinoma and triple negative breast cancer in 2017. Our second product candidate, CB-1158, is a first-in-class oral inhibitor of arginase, an enzyme that depletes the amino acid arginine, a key metabolic nutrient for T cells, and is being co-developed with Incyte Pharmaceuticals for hematology and oncology indications. CB-1158 is currently being tested alone and in combination with a checkpoint inhibitor in a Phase 1/2 clinical trial in patients with solid tumors. We also have ongoing research efforts that are focused on discovering additional product candidates against novel tumor metabolism and immunology targets.

Our lead product candidate, CB-839, takes advantage of the pronounced dependency many cancers have on the nutrient glutamine for growth and survival. CB-839 inhibits glutaminase, an enzyme required by cancer cells to utilize glutamine effectively. In preclinical studies, CB-839 demonstrated broad antitumor activity in tumor cell lines, inhibited the growth of human tumors in animal models and was well tolerated in toxicity studies. CB-839 was also synergistic with several approved, standard of care, cancer therapeutics. We believe CB-839 has the potential to be an important new therapeutic agent with a novel mechanism of action for the treatment of a broad range of cancers, and is the only selective glutaminase inhibitor currently in clinical trials. We currently retain all commercial rights to CB-839 and have been granted a U.S. patent, which includes composition of matter coverage for CB-839 through 2032.

CB-839 may also have the potential to work in combination with immuno-oncology (I-O) therapeutics. Inhibition of glutaminase results in accumulation of glutamine, the substrate of glutaminase, in tumors. Glutamine, which is frequently depleted in the tumor microenvironment due to avid uptake by tumor cells, has been shown to be an important nutrient for T-cell proliferation. Administration of CB-839 to tumor-bearing animals substantially enhances the anti-tumor activity of checkpoint inhibitors, potentially by restoring the levels of glutamine in the tumor microenvironment and thereby enabling T-cells to proliferate. Checkpoint inhibitors, including the approved agents nivolumab (marketed as Opdivo) and pembrolizumab (marketed as Keytruda), are a class of immuno-oncology agents

directed against programmed death protein-1 (PD-1) or programmed death ligand-1 (PD-L1) that promote the activation and tumor-killing properties of the patient's own immune cells, such as cytotoxic T-cells. CB-839 could potentially have multiple mechanisms of action in the treatment of cancer first by starving the tumor cell, and second by facilitating the activation of T-cells in the nutrient-deprived tumor microenvironment.

Our second product candidate, CB-1158, is a potent and selective orally bioavailable inhibitor of the enzyme arginase, that was discovered at Calithera and is being co-developed with Incyte Corporation. Arginase depletes arginine, a nutrient that is critical for the activation and proliferation of the body's cancer-fighting immune cells, such as cytotoxic T-cells and natural killer (NK)-cells. During normal activation of the immune system, arginase, which is expressed by suppressive myeloid immune cells, plays an important role in halting T-cell proliferation. But in many tumors, including lung, gastrointestinal, bladder, renal cancer and acute myeloid leukemia, arginase-expressing myeloid cells accumulate and maintain an immunosuppressive environment, blocking the ability of T-cells and NK-cells to kill cancer cells. We believe that inhibitors of arginase can promote an anti-tumor immune response by restoring arginine levels, thereby allowing activation of the body's own immune cells, including cytotoxic T-cells and NK-cells.

Critical Accounting Policies and Estimates

Our management's discussion and analysis of our financial condition and results of operations is based on our financial statements, which have been prepared in accordance with United States generally accepted accounting principles, or U.S. GAAP. The preparation of these financial statements requires us to make estimates and assumptions that affect the reported amounts of assets and liabilities and the disclosure of contingent assets and liabilities at the date of the financial statements, as well as the reported expenses incurred during the reporting periods. Our estimates are based on our historical experience and on various other factors that we believe are reasonable under the circumstances, the results of which form the basis for making judgments about the carrying value of assets and liabilities that are not readily apparent from other sources. Actual results may differ from these estimates under different assumptions or conditions. We believe that the accounting policies discussed below are critical to understanding our historical and future performance, as these policies relate to the more significant areas involving management's judgments and estimates.

Accrued Research and Development Costs

We record accrued liabilities for estimated costs of our research and development activities conducted by third-party service providers, which include the conduct of preclinical studies and clinical trials and contract manufacturing activities. We record the estimated costs of research and development activities based upon the estimated amount of services provided but not yet invoiced, and include these costs in accrued liabilities in the balance sheet and within research and development expense in the statement of operations. These costs are a significant component of our research and development expenses. We record accrued expenses for these costs based on the estimated amount of work completed and in accordance with agreements established with these third parties.

We estimate the amount of work completed through discussions with internal personnel and external service providers as to the progress or stage of completion of the services and the agreed-upon fee to be paid for such services. We make significant judgments and estimates in determining the accrued balance in each reporting period. As actual costs become known, we adjust our accrued estimates. Although we do not expect our estimates to be materially different from amounts actually incurred, our understanding of the status and timing of services performed, the number of patients enrolled, and the rate of patient enrollment may vary from our estimates and could result in us reporting amounts that are too high or too low in any particular period. Our accrued expenses are dependent, in part, upon the receipt of timely and accurate reporting from clinical research organizations and other third-party service providers. To date, there have been no material differences from our accrued expenses to actual expenses.

Stock-Based Compensation

We recognize compensation costs related to stock options granted to employees based on the estimated fair value of the awards on the date of grant, net of estimated forfeitures. We estimate the grant date fair value, and the resulting stock-based compensation expense, using the Black-Scholes option-pricing model. The grant date fair value of the stock-based awards is generally recognized on a straight-line basis over the requisite service period, which is generally the vesting period of the respective awards.

The Black-Scholes option-pricing model requires the use of highly subjective assumptions, which determine the fair value of stock-based awards. These assumptions include:

Expected Term. Our expected term represents the period that our stock-based awards are expected to be outstanding and is determined using the simplified method (based on the mid-point between the vesting date and the end of the contractual term).

Expected Volatility. Since we have only been publicly traded for a short period and do not have adequate trading history for our common stock, the expected volatility was estimated based on the average volatility for comparable publicly traded biopharmaceutical companies over a period equal to the expected term of the stock option grants. The comparable companies were chosen based on their similar size, stage in the life cycle, or area of specialty.

Risk-Free Interest Rate. The risk-free interest rate is based on the U.S. Treasury zero coupon issues in effect at the time of grant for periods corresponding with the expected term of option.

Expected Dividend. We have never paid dividends on our common stock and have no plans to pay dividends on our common stock. Therefore, we used an expected dividend yield of zero.

In addition to the Black-Scholes assumptions, we estimate our forfeiture rate based on an analysis of our actual forfeitures and will continue to evaluate the adequacy of the forfeiture rate based on actual forfeiture experience, analysis of employee turnover behavior, and other factors. The impact from any forfeiture rate adjustment would be recognized in full in the period of adjustment and if the actual number of future forfeitures differs from our estimates, we might be required to record adjustments to stock-based compensation in future periods.

Prior to our IPO in October 2014, the fair value of the shares of common stock underlying our share-based awards were estimated on each grant date by our Board of Directors. In order to determine the fair value of our common stock underlying option grants, our Board of Directors considered, among other things, timely valuations of our common stock prepared by an unrelated third-party valuation firm in accordance with the guidance provided by the American Institute of Certified Public Accountants Practice Guide, Valuation of Privately-Held-Company Equity Securities Issued as Compensation. Given the absence of a public trading market for our common stock, our Board of Directors exercised reasonable judgment and considered a number of objective and subjective factors to determine the best estimate of the fair value of our common stock, including our stage of development; progress of our research and development efforts; the rights, preferences and privileges of our preferred stock relative to those of our common stock; equity market conditions affecting comparable public companies and the lack of marketability of our common stock. After the closing of our IPO, our Board of Directors determines the fair value of each share of underlying common stock based on the closing price of our common stock as reported by the NASDAQ Select Global Market on the date of grant.

Income Taxes

As of December 31, 2016, we had approximately \$108.8 million and \$48.0 million, respectively, of federal and state operating loss carryforwards available to reduce future taxable income that will begin to expire in 2030 for federal and state tax purposes.

As of December 31, 2016, we also had research and development tax credit carryforwards of approximately \$3.4 million and \$2.5 million, respectively, for federal and state purposes available to offset future taxable income tax. If not utilized, the federal carryforwards will expire in various amounts beginning in 2030, and the state credits can be carried forward indefinitely.

Utilization of the net operating loss carryforwards may be subject to a substantial annual limitation due to the ownership change limitations provided by the Internal Revenue Code of 1986, as amended, and similar state provisions. We have performed an analysis to determine whether an "ownership change" has occurred from inception to December 31, 2014. Based on this analysis, management has determined that there was an ownership change. The annual limitation may result in the expiration of net operating losses and credits before utilization, however, we do not believe any of our net operating losses and research and development credits are limited by this potential ownership change.

Financial Operations Overview

Research and Development Expenses

Research and development expenses represent costs incurred to conduct research, such as the discovery and development of our product candidates. We recognize all research and development costs as they are incurred. Research and development expenses consist primarily of the following:

- employee-related expenses, which include salaries, benefits and stock-based compensation;
- expenses incurred under agreements with clinical trial sites that conduct research and development activities on our behalf;
- laboratory and vendor expenses related to the execution of preclinical studies and clinical trials;
- contract manufacturing expenses, primarily for the production of clinical supplies;
- facilities and other allocated expenses, which include direct and allocated expenses for rent and maintenance of facilities, depreciation and amortization expense and other supplies; and
- license fees and milestone payments related to our licensing agreements.

The largest component of our total operating expenses has historically been our investment in research and development activities including the clinical development of our product candidates. We allocate to research and development expenses the salaries, benefits, stock-based compensation expense, and indirect costs of our clinical and preclinical programs on a program-specific basis, and we include these costs in the program-specific expenses. The following table shows our research and development expenses for 2016, 2015, and 2014:

	Year Ended December 31,		
	2016	2015	2014
	(in thousands)		
Development candidate:			
CB-839 (Glutaminase inhibitor)	\$11,355	\$13,279	\$12,381
CB-1158 (Arginase inhibitor)	11,596	\$—	
Total development	22,951	13,279	12,381
Preclinical and research:			
Arginase inhibitors	722	9,329	3,461
Other preclinical and research	4,075	1,140	525
Total preclinical and research	4,797	10,469	3,986
Total	\$27,748	\$23,748	\$16,367

We expect our research and development expenses will increase during the next few years as we advance our product candidates into and through clinical trials, pursue regulatory approval of our product candidates, which will require a significant investment in contract manufacturing and inventory build-up related costs.

The process of conducting clinical trials necessary to obtain regulatory approval is costly and time consuming. We may never succeed in achieving marketing approval for our product candidates. The probability of success of our product candidates may be affected by numerous factors, including clinical data, competition, manufacturing capability and commercial viability. As a result, we are unable to determine the duration and completion costs of our research and development projects or when and to what extent we will generate revenue from the commercialization and sale of any of our product candidates.

General and Administrative Expenses

General and administrative expenses consist of personnel costs, allocated expenses and other expenses for outside professional services, including legal, audit and accounting services. Personnel costs consist of salaries, benefits and stock-based compensation. Allocated expenses consist of facilities and other allocated expenses, which include direct and allocated expenses for rent and maintenance of facilities, depreciation and amortization expense and other supplies. We have incurred and expect to continue to incur additional expenses as a result of operating as a public company, including costs to comply with the rules and regulations applicable to companies listed on a national securities exchange and costs related to compliance and reporting obligations pursuant to the rules and regulations of the SEC, particularly after we cease to be an “emerging growth company.” In addition, we have incurred and expect to continue to incur increased expenses associated with being a public company, including additional insurance, investor relations and other increases related to needs for additional human resources and professional services.

Results of Operations

Comparison of the Years Ended December 31, 2016 and 2015

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	Years Ended		Change	
	December 31, 2016	2015	\$	%
(in thousands, except percentages)				
Operating expenses:				
Research and development	\$27,748	\$23,748	\$4,000	17%
General and administrative	10,586	9,071	1,515	17%
Total operating expenses	38,334	32,819	5,515	17%
Loss from operations	(38,334)	(32,819)	(5,515)	17%
Interest income, net	330	175	155	89%
Net loss	\$(38,004)	\$(32,644)	\$(5,360)	16%

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Research and Development

Research and development expenses increased \$4.0 million, or 17%, from \$23.7 million for 2015 to \$27.7 million for 2016. The increase was due to an increase of \$2.3 million in personnel-related costs primarily as a result of higher headcount, salary increases and stock-based compensation expenses, an increase of \$1.1 million primarily related to increased preclinical development and manufacturing activities in support of our arginase inhibitors program, and an increase of \$0.8 million in clinical trial related expenses in connection with our CB-839 and CB-1158 Phase 1 clinical trials, partially offset by a decrease of \$0.2 million related to fees under our licensing arrangements.

General and Administrative

General and administrative expenses increased \$1.5 million, or 17%, from \$9.1 million for 2015 to \$10.6 million for 2016. The increase was due to an increase of \$1.2 million in personnel-related costs as a result of higher headcount, salary increases and stock-based compensation expense, \$0.3 million due to a one-time severance charge related to a former employee, and an increase of \$0.2 million in professional services costs primarily related to legal costs to support our patent portfolio, partially offset by a decrease of \$0.2 million for a payment to a third party related to a terminated license arrangement.

Comparison of the Years Ended December 31, 2015 and 2014

	Year Ended		Change	
	December 31, 2015	2014	\$	%
	(in thousands, except percentages)			
Operating expenses:				
Research and development	\$23,748	\$16,367	\$7,381	45%
General and administrative	9,071	5,354	3,717	69%
Total operating expenses	32,819	21,721	11,098	51%
Loss from operations	(32,819)	(21,721)	(11,098)	51%
Interest income, net	\$175	\$9	166	*
Net loss	\$(32,644)	\$(21,712)	\$(10,932)	50%

* Percentage not meaningful.

Research and Development

Research and development expenses increased \$7.4 million, or 45%, from \$16.4 million for 2014 to \$23.7 million for 2015. The increase was due to an increase of \$3.0 million in personnel-related costs primarily as a result of higher headcount, salary increases and stock-based compensation expenses, an increase of \$2.5 million primarily related to increased preclinical development activities in our arginase inhibitors program, an increase of \$1.3 million in clinical trial related expenses in connection with our CB-839 Phase 1 clinical trials, and an increase of \$0.6 million related to our licensing arrangement for our hexokinase II inhibitors program.

General and Administrative

General and administrative expenses increased \$3.7 million, or 69%, from \$5.4 million for 2014, to \$9.1 million for 2015. The increase was due to an increase of \$2.2 million in personnel-related costs as a result of higher headcount, salary increases and stock-based compensation expense, an increase of \$1.3 million in professional services costs primarily related to legal and insurance costs associated with operating as a public company, and an increase of \$0.2 million for a payment to a third party related to a terminated license arrangement.

Liquidity and Capital Resources

As of December 31, 2016, we had cash, cash equivalents and investments totaling \$51.8 million. Subsequent to December 31, 2016, we received:

- \$45.0 million as an upfront license fee payment pursuant to our global collaboration and license agreement with Incyte;
- \$8.0 million in gross proceeds, \$7.9 million in net proceeds after deducting offering expenses, from the sale of our common stock pursuant to our stock purchase agreement with Incyte;
- \$38.0 million in gross proceeds, \$36.9 million in net proceeds after deducting underwriters fees and offering expenses, from the sale of our common stock pursuant to our at-the-market offering program with Cowen and Company LLC, or Cowen.

In November 2015 we filed a registration statement on Form S-3 with the Securities and Exchange Commission which permits the offering, issuance and sale by us of up to a maximum aggregate offering price of \$150.0 million of our common stock. Up to \$50.0 million of the maximum aggregate offering price of \$150.0 million may be issued and sold pursuant to an at-the-market offering program, or ATM, for sales of our common stock under a sales agreement with Cowen, which would act as our sales agent and underwriter. As of March 16, 2017, \$92.0 million of common stock remains available for issuance, none of which may be issued pursuant to our ATM.

Our primary uses of cash are to fund operating expenses, primarily research and development expenditures. Cash used to fund operating expenses is impacted by the timing of when we pay these expenses, as reflected in the change in our outstanding accounts payable and accrued expenses.

We believe that our existing cash, cash equivalents and investments as of December 31, 2016 will be sufficient for us to meet our current operating plan for at least the next twelve months. However, our forecast of the period of time through which our financial resources will be adequate to support our operations is a forward-looking statement that involves risks and uncertainties, and actual results could vary materially. In order to complete the process of obtaining regulatory approval for our product candidates and to build the sales, marketing and distribution infrastructure that we believe will be necessary to commercialize our product candidates, if approved, we will require substantial additional funding.

We have based our projections of operating capital requirements on assumptions that may prove to be incorrect and we may use all of our available capital resources sooner than we expect. Because of the numerous risks and uncertainties associated with research, development and commercialization of pharmaceutical products, we are unable to estimate the exact amount of our operating capital requirements. Our future funding requirements will depend on many factors, including, but not limited to:

- the timing and costs of our planned clinical trials for our product candidates;
- the timing and costs of our planned preclinical studies of our product candidates;
- our success in establishing and scaling commercial manufacturing capabilities;
- the number and characteristics of product candidates that we pursue;
- the outcome, timing and costs of seeking regulatory approvals;
- subject to receipt of regulatory approval, revenue received from commercial sales of our product candidates;
- the terms and timing of any future collaborations, licensing, consulting or other arrangements that we may establish;
- the amount and timing of any payments we may be required to make in connection with the licensing, filing, prosecution, maintenance, defense and enforcement of any patents or patent applications or other intellectual property rights; and
- the extent to which we in-license or acquire other products and technologies.

We plan to continue to fund our operations and capital funding needs through equity and/or debt financing. We may also consider collaborations or selectively partnering for clinical development and commercialization. The sale of additional equity would result in additional dilution to our stockholders. The incurrence of debt financing would result in debt service obligations and the instruments governing such debt could provide for operating and financing covenants that would restrict our operations. If we are not able to secure adequate additional funding we may be forced to make reductions in spending, extend payment terms with suppliers, liquidate assets where possible, and/or suspend or curtail planned programs. Any of these actions could harm our business, results of operations and future prospects.

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

	Year Ended December 31,		
	2016	2015	2014
	(in thousands)		
Cash used in operating activities	\$(31,025)	\$(29,933)	\$(19,231)
Cash provided by (used in) investing activities	\$23,705	\$(66,776)	\$(486)
Cash provided by financing activities	\$11,816	\$845	\$87,866

Cash Flows from Operating Activities

Cash used in operating activities for the year ended December 31, 2016 was \$31.0 million, consisting of a net loss of \$38.0 million, which was offset by non-cash charges \$0.9 million for depreciation and amortization expense and \$4.3 million for stock-based compensation. The change in our net operating assets and liabilities of \$1.8 million was primarily due to the timing of payments for our clinical trial and manufacturing activities.

Cash used in operating activities for the year ended December 31, 2015 was \$29.9 million, consisting of a net loss of \$32.6 million, which was offset by non-cash charges \$0.9 million for depreciation and amortization expense and \$3.3 million for stock-based compensation. The change in our net operating assets and liabilities of \$1.4 million was primarily due to the timing of payments for our clinical trial and manufacturing activities.

Cash used in operating activities for the year ended December 31, 2014 was \$19.2 million, consisting of a net loss of \$21.7 million, which was offset by non-cash charges \$0.4 million for depreciation and amortization expense and \$0.7 million for stock-based compensation. The change in our net operating assets and liabilities was primarily due to a \$1.5 million increase in prepaid expenses and other current assets primarily related to our prepayment of clinical trial activities and directors and officers liability insurance, a \$2.6 million increase in accounts payable and accrued liabilities related to an increase in our research and development activities, and a \$0.4 million increase in deferred rent.

Cash Flows from Investing Activities

Cash provided by investing activities for the year ended December 31, 2016 was \$23.7 million and was related to the sale or maturity of investments of \$68.7 million, offset by the purchase of investments of \$44.6 million and purchase of property and equipment of \$0.4 million.

Cash used in investing activities for the year ended December 31, 2015 was \$66.8 million and was related to the purchase of investments of \$109.1 million and purchase of property and equipment of \$0.4 million, offset by the sale or maturity of investments of \$42.8 million.

Cash used in investing activities for the year ended December 31, 2014 was \$0.5 million and was related the purchase of property and equipment of \$0.6 million, offset by the reduction in restricted cash of \$70,000. Purchases of property and equipment were primarily related to leasehold improvements in connection with our office expansion.

Cash Flows from Financing Activities

Cash provided by financing activities for the year ended December 31, 2016 was \$11.8 million and was from the issuance of common stock through an at-the-market offering program of \$11.3 million and from the issuance of common stock upon the exercise of stock options and employee stock plan purchases of \$0.5 million.

Cash provided by financing activities for the year ended December 31, 2015 was \$0.8 million and was from the issuance of common stock upon the exercise of stock options and employee stock plan purchases.

Cash provided by financing activities for the year ended December 31, 2014 was \$87.9 million and was related to net proceeds of \$71.6 million from the sale of our common stock, upon our initial public offering in October 2014, \$16.0 million in net proceeds from the sale and issuance of preferred stock, and \$0.3 million from the issuance of common stock upon the exercise of stock options.

Contractual Obligations and Other Commitments

The following table summarizes our contractual obligations as of December 31, 2016:

Contractual Obligations:	Payments Due By Period				Total
	Less Than 1 Year	1 to 3 Years	3 to 5 Years	More Than 5 Years	
	(In thousands)				
Operating lease obligations ⁽¹⁾	\$1,831	\$4,316	\$4,755	\$5,264	\$16,166
Less: sublease income ⁽²⁾	(880)	(2,198)	(187)	-	(3,265)
Total contractual obligations ⁽³⁾	\$951	\$2,118	\$4,568	\$5,264	\$12,901

1. Represents future minimum lease payments under the non-cancelable lease for our headquarters in South San Francisco, California. The minimum lease payments above do not include any related common area maintenance charges or real estate taxes.

2. In February 2017, we entered into a non-cancelable sublease agreement for a portion of our facilities, from March 2017 through February 2020.

3. We enter into agreements in the normal course of business with organizations for collaborations or in-licensing arrangements, contract research organizations for clinical trials and vendors for preclinical studies and other services and products for operating purposes which are cancelable at any time by us, generally upon 30 to 60 days prior written notice. These payments are not included in this table of contractual obligations.

Off-Balance Sheet Arrangements

During 2016, 2015, and 2014 we did not have any off-balance sheet arrangements.

JOBS Act Accounting Election

We are an “emerging growth company,” as defined in the JOBS Act. Under the JOBS Act, emerging growth companies can delay adopting new or revised accounting standards issued subsequent to the enactment of the JOBS Act until such time as those standards apply to private companies. We have irrevocably elected not to avail ourselves of this exemption from new or revised accounting standards, and, therefore, are subject to the same new or revised accounting standards as other public companies that are not emerging growth companies.

Recent Accounting Pronouncements

In May 2014, the Financial Accounting Standards Board (FASB) issued Auditing Standards Update, or ASU, No. 2014-09, Revenue from Contracts with Customers (Topic 606). This ASU affects any entity that either enters into contracts with customers to transfer goods and services or enters into contracts for the transfer of nonfinancial assets. ASU 2014-09 will replace most existing revenue recognition guidance in U.S. GAAP when it becomes effective. The standard’s core principle is that a company will recognize revenue when it transfers promised goods or services to customers in an amount that reflects the consideration to which it expects to be entitled in exchange for those goods or services. In doing so, companies will need to use more judgment and make more estimates than under the currently effective guidance. These may include identifying performance obligations in the contract, estimating the amount of variable consideration to include in the transaction price and allocating the transaction price to each separate performance obligation. In April 2016, the FASB issued ASU No. 2016-10, Revenue from Contracts with Customers

(Topic 606): Identifying Performance Obligations and Licensing, which reduces the complexity when applying the guidance for identifying performance obligations and improves the operability and understandability of the license implementation guidance. In May 2016, the FASB issued ASU No. 2016-12, Revenue from Contracts with Customers (Topic 606): Narrow-Scope Improvements and Practical Expedients, which amends the guidance on transition, collectability, noncash consideration and the presentation of sales and other similar taxes. The new standard permits adoption either by using (i) a full retrospective approach for all periods presented in the period of adoption or (ii) a modified retrospective approach with the cumulative effect of initially applying the new standard recognized at the date of initial application and providing certain additional disclosures. The new standard is effective for annual reporting periods beginning after December 15, 2017, with early adoption permitted for annual reporting periods beginning after December 15, 2016. The Company plans to adopt the new standard effective January 1, 2018 and has not made the decision as to which adoption method it will utilize. The Company's final determination will depend on the significance of the impact of the new standard on the Company's financial results. As of December 31, 2016, the Company has not recognized any revenues to date.

In August 2014, the FASB issued Accounting Standards Update (ASU) No. 2014-15, Disclosure of Uncertainties about an Entity's Ability to Continue as a Going Concern. ASU 2014-15 requires management to evaluate whether there is substantial doubt about an entity's ability to continue as a going concern and to provide related footnote disclosures. In doing so, companies will have reduced diversity in the timing and content of footnote disclosures than under today's guidance. ASU 2014-15 is effective for the Company for the 2016 annual period and with early adoption permitted. The Company adopted ASU 2014-15 effective December 31, 2016.

In February 2016, the FASB issued ASU 2016-02, Leases. The ASU requires management to recognize lease assets and lease liabilities by lessees for all operating leases. The ASU is effective for periods ending on December 15, 2018 and interim periods therein on a modified retrospective basis. The Company is currently assessing the impact the adoption of ASU 2016-02 will have on the financial statements.

In March 2016, the FASB issued ASU 2016-09, Compensation – Stock Compensation. ASU 2016-09 simplified certain aspects of the accounting for share-based payment transactions, including income taxes, classification of awards and classification in the statement of cash flows. ASU 2016-09 is effective for the annual period beginning after December 15, 2016, and interim periods therein. The Company is currently assessing the impact of adopting ASU 2016-09 will have on its financial statements.

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

We are exposed to market risks in the ordinary course of our business. These risks primarily include interest rate sensitivities. Our investment policy allows us to maintain a portfolio of cash equivalents and investments in a variety of high credit quality securities issued by the U.S. government, U.S. government-sponsored agencies and highly rated banks and corporations, subject to certain concentration limits. Our investment policy prohibits us from holding auction rate securities or derivative financial instruments. As of December 31, 2016, we had cash, cash equivalents and investments of \$51.8 million. A portion of our investments may be subject to interest rate risk and could fall in value if market interest rates increase. However, we believe that our exposure to interest rate risk is not significant as the majority of our investments are short-term in duration and a 1% change in interest rates would not have a significant impact on the total value of our portfolio. We actively monitor changes in interest rates. We had no outstanding debt as of December 31, 2016.

Item 8. Financial Statements and Supplementary Data.
CALITHERA BIOSCIENCES, INC.

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Report of Independent Registered Public Accounting Firm

The Board of Directors and Stockholders of Calithera Biosciences, Inc.

We have audited the accompanying balance sheets of Calithera Biosciences, Inc. as of December 31, 2016 and 2015, and the related statements of operations, comprehensive loss, convertible preferred stock and stockholder's equity (deficit) and cash flows for each of the three years in the period ended December 31, 2016. These financial statements are the responsibility of the Company's management. Our responsibility is to express an opinion on these financial statements based on our audits.

We conducted our audits in accordance with the standards of the Public Company Accounting Oversight Board (United States). Those standards require that we plan and perform the audit to obtain reasonable assurance about whether the financial statements are free of material misstatement. We were not engaged to perform an audit of the Company's internal control over financial reporting. Our audits included consideration of internal control over financial reporting as a basis for designing audit procedures that are appropriate in the circumstances, but not for the purpose of expressing an opinion on the effectiveness of the Company's internal control over financial reporting. Accordingly, we express no such opinion. An audit also includes examining, on a test basis, evidence supporting the amounts and disclosures in the financial statements, assessing the accounting principles used and significant estimates made by management, and evaluating the overall financial statement presentation. We believe that our audits provide a reasonable basis for our opinion.

In our opinion, the financial statements referred to above present fairly, in all material respects, the financial position of Calithera Biosciences, Inc. at December 31, 2016 and 2015, and the results of its operations and its cash flows for each of the three years in the period ended December 31, 2016, in conformity with U.S. generally accepted accounting principles.

/s/ Ernst & Young LLP

Redwood City, California

March 16, 2017

Calithera Biosciences, Inc.

Balance Sheets

(in thousands, except per share amounts)

	December 31,	
	2016	2015
Assets		
Current assets:		
Cash and cash equivalents	\$ 10,601	\$ 6,105
Short-term investments	41,180	63,823
Prepaid expenses and other current assets	1,780	2,567
Total current assets	53,561	72,495
Long-term investments	-	1,997
Restricted cash	46	46
Property and equipment, net	899	931
Other assets	290	281
Total assets	\$ 54,796	\$ 75,750
Liabilities and Stockholders' Equity		
Current liabilities:		
Accounts payable	\$ 398	\$ 562
Accrued liabilities	4,055	3,271
Total current liabilities	4,453	3,833
Deferred rent	437	129
Total liabilities	4,890	3,962
Commitments and contingencies (Note 5)		
Stockholders' equity:		
Preferred stock, \$0.0001 par value per share, 10,000 shares authorized as of		
December 31, 2016 and 2015; no share issued and outstanding as of		
December 31, 2016 and 2015		
	-	-
Common stock, \$0.0001 par value, 200,000 shares authorized as of		
December 31, 2016 and 2015; 21,502 and 18,232 shares		
issued and outstanding as of December 31, 2016 and 2015, respectively		
	2	2
Additional paid-in capital	172,419	156,353
Accumulated deficit	(122,502)	(84,498)
Accumulated other comprehensive loss	(13)	(69)
Total stockholders' equity	49,906	71,788
Total liabilities and stock and stockholders' equity	\$ 54,796	\$ 75,750

See accompanying notes.

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Calithera Biosciences, Inc.

Statements of Operations

(in thousands, except per share amounts)

	Year Ended December 31,		
	2016	2015	2014
Operating expenses:			
Research and development	\$27,748	\$23,748	\$16,367
General and administrative	10,586	9,071	5,354
Total operating expenses	38,334	32,819	21,721
Loss from operations	(38,334)	(32,819)	(21,721)
Interest income, net	330	175	9
Net loss	(38,004)	(32,644)	(21,712)
Net loss per share, basic and diluted	\$(1.95)	\$(1.81)	\$(4.67)
Weighted average common shares used to compute			
net loss per share, basic and diluted	19,486	18,045	4,652

See accompanying notes.

Calithera Biosciences, Inc.

Statements of Comprehensive Loss

(in thousands)

	Year Ended December 31,		
	2016	2015	2014
Net loss	\$(38,004)	\$(32,644)	\$(21,712)
Other comprehensive gain (loss):			
Net unrealized gain (loss) on available-for-sale securities	56	(69)	—
Total comprehensive loss	\$(37,948)	\$(32,713)	\$(21,712)

See accompanying notes.

Calithera Biosciences, Inc.

Statements of Convertible Preferred Stock and Stockholders' Equity (Deficit)

(in thousands, except per share amounts)

	Convertible Shares	Preferred Amount	Common Stock Shares	Common Amount	Additional Paid-In Capital	Accumulated Deficit	Other Comprehensive Income	Total Stockholders' Equity (Deficit)
Balance at December 31, 2013	7,689	\$ 54,282	161	\$ -	\$ 9,329	\$ (30,142)	\$ -	\$ (20,813)
Issuance of Series D convertible preferred stock for cash at \$8.41 per share in July 2014, net of \$41 in issuance costs	1,903	15,959	-	-	-	-	-	-
Conversion of preferred stock to common stock upon initial public offering	(9,592)	(70,241)	9,592	1	70,240	-	-	70,241
Issuance of common stock in connection with initial public offering, net of underwriting discounts, commissions and issuance costs	-	-	8,000	1	71,623	-	-	71,624
Issuance of common stock to nonemployees	-	-	21	-	54	-	-	54
Vesting of common stock issued to founders	-	-	1	-	1	-	-	1
Exercise of stock options	-	-	168	-	282	-	-	282
Stock-based compensation expense	-	-	-	-	689	-	-	689
Net loss	-	-	-	-	-	(21,712)	-	(21,712)
Balance at December 31, 2014	-	-	17,943	2	152,218	(51,854)	-	100,366
Exercise of stock options	-	-	219	-	365	-	-	365
Issuance of common stock per ESPP purchase	-	-	70	-	498	-	-	498
Stock-based compensation expense	-	-	-	-	3,272	-	-	3,272
Net loss	-	-	-	-	-	(32,644)	-	(32,644)
Unrealized loss on available-for-sale securities	-	-	-	-	-	-	(69)	(69)
	-	-	18,232	2	156,353	(84,498)	(69)	71,788

Balance at December 31, 2015								
Issuance of common stock in connection with at-the-market offering, net of underwriting commissions and issuance costs	-	-	3,059	-	11,281	-	-	11,281
Exercise of stock options	-	-	99	-	177	-	-	177
Issuance of common stock per ESPP purchase	-	-	112	-	358	-	-	358
Stock-based compensation expense	-	-	-	-	4,250	-	-	4,250
Net loss	-	-	-	-	-	(38,004)	-	(38,004)
Unrealized gain on available-for-sale securities	-	-	-	-	-	-	56	56
Balance at December 31, 2016	-	\$-	21,502	\$ 2	\$172,419	\$ (122,502)	\$ (13)	\$ 49,906

See accompanying notes.

Calithera Biosciences, Inc.

Statements of Cash Flows

(in thousands)

	Year Ended December 31,		
	2016	2015	2014
Cash Flows From Operating Activities			
Net loss	\$(38,004)	\$(32,644)	\$(21,712)
Adjustments to reconcile net loss to net cash used in operating activities:			
Depreciation and amortization	297	404	361
Amortization of premiums on investments	590	446	—
Stock-based compensation	4,250	3,272	689
(Gain) Loss on disposal of property and equipment	—	(7)	2
Changes in operating assets and liabilities:			
Prepaid expenses and other current assets	787	(673)	(1,544)
Other assets	(9)	(263)	—
Accounts payable	(28)	(131)	543
Accrued liabilities	925	(196)	2,058
Deferred rent, non-current	167	(141)	372
Net cash used in operating activities	(31,025)	(29,933)	(19,231)
Cash Flows From Investing Activities			
Purchases of investments	(44,618)	(109,099)	—
Proceeds from the sales or maturity of investments	68,724	42,764	—
Purchase of property and equipment	(401)	(441)	(556)
Change in restricted cash	—	—	70
Net cash provided by (used in) investing activities	23,705	(66,776)	(486)
Cash Flows From Financing Activities			
Proceeds from issuance of common stock upon initial public offering, net	—	—	71,625
Proceeds from issuance of common stock through an at-the-market offering, net	11,281	—	—
Proceeds from issuance of convertible preferred stock, net	—	—	15,959
Proceeds from stock option exercises and employee stock plan purchases	535	845	282
Net cash provided by financing activities	11,816	845	87,866
Net increase (decrease) in cash and cash equivalents	4,496	(95,864)	68,149
Cash and cash equivalents at beginning of period	6,105	101,969	33,820
Cash and cash equivalents at end of period	\$10,601	\$6,105	\$101,969
Supplemental Disclosure of Non-Cash Investing and Financing Information:			
Unpaid amounts related to property and equipment purchases	\$—	\$26	\$110
Services settled through the issuance of common stock	\$—	\$—	\$55

See accompanying notes.

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Calithera Biosciences, Inc.

Notes to Financial Statements

1. Organization and Basis of Presentation

Calithera Biosciences, Inc. (the “Company”) was incorporated in the State of Delaware on March 9, 2010. The Company is a clinical-stage biopharmaceutical company focused on discovering and developing novel small molecule drugs directed against tumor metabolism and tumor immunology targets for the treatment of cancer. The Company’s principal operations are based in South San Francisco, California, and it operates in one segment.

Liquidity

In the course of its development activities, the Company has sustained operating losses and expects such losses to continue over the next several years. The Company’s ultimate success depends on the outcome of its research and development activities. The Company has incurred net losses from operations since inception and has an accumulated deficit of \$122.5 million as of December 31, 2016. The Company intends to raise additional capital through the issuance of additional equity, and potentially through strategic alliances with partner companies. However, if such financing is not available at adequate levels, the Company will need to reevaluate its operating plans. Management believes that the currently available resources will provide sufficient funds to enable the Company to meet its operating plan for at least the twelve month period following the filing of the Company’s financial statement on Form 10-K. However, if the Company’s anticipated operating results are not achieved in future periods, management believes that planned expenditures may need to be reduced in order to extend the time period over which the then-available resources would be able to fund the Company’s operations.

2. Summary of Significant Accounting Policies

Use of Estimates

The accompanying financial statements have been prepared in accordance with U.S. generally accepted accounting principles (“GAAP”). The preparation of financial statements in conformity with GAAP requires management to make estimates and assumptions that affect the reported amounts of assets and liabilities and disclosure of contingent assets and liabilities as of the date of the financial statements and the reported amounts of revenue and expenses during the reporting period. On an ongoing basis, management evaluates its estimates, including those related to clinical trial accrued liabilities, fair value of common stock, fair value of marketable securities, income taxes, and stock-based compensation. Management bases its estimates on historical experience and on various other market specific and relevant assumptions that management believes to be reasonable under the circumstances. Actual results could differ from those estimates.

Cash and Cash Equivalents

The Company considers all highly liquid investments with original maturities of three months or less at the time from the date of purchase to be cash equivalents. Cash equivalents, which consist primarily of amounts invested in money market accounts, are stated at fair value.

Investments

All investments have been classified as “available-for-sale” and are carried at estimated fair value as determined based upon quoted market prices or pricing models for similar securities. Management determines the appropriate classification of its investments at the time of purchase and reevaluates such designation as of each balance sheet date. Unrealized gains and losses are excluded from earnings and are reported as a component of comprehensive loss. Realized gains and losses and declines in fair value judged to be other than temporary, if any, on available-for-sale securities are included in interest income, net. The cost of securities sold is based on the specific-identification method. Interest on marketable securities is included in interest income, net.

Restricted Cash

Restricted cash consists of money market funds held by the Company’s financial institution as collateral for the Company’s obligations under its facility lease for the Company’s corporate headquarters in South San Francisco, California.

Concentration of Credit Risk

Financial instruments that potentially subject the Company to a concentration of credit risk consist of cash, cash equivalents, investments and restricted cash. The Company invests in a variety of financial instruments and, by its policy, limits these financial

instruments to high credit quality securities issued by the U.S. government, U.S. government-sponsored agencies and highly rated banks and corporations, subject to certain concentration limits. The Company's cash, cash equivalents, investments and restricted cash are held by financial institutions in the United States that management believes are of high credit quality. Amounts on deposit may at times exceed federally insured limits.

Property and Equipment

Property and equipment are stated at cost, less accumulated depreciation and amortization. Depreciation and amortization is computed using the straight-line method over the estimated useful lives of the respective assets. Depreciation and amortization begins at the time the asset is placed in service. Maintenance and repairs are charged to operations as incurred. Upon sale or retirement of assets, the cost and related accumulated depreciation and amortization are removed from the balance sheet and the resulting gain or loss is reflected in operations.

The useful lives of property and equipment are as follows:

Research and development