2020 Annual Report

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, 2020

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

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	CALA	The Nasdaq Global Select Market
(Title of each class)	(Trading Symbol)	(Name of each exchange on which registered)

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 every Interactive Data File required to be submitted pursuant to Rule 405 of Regulation S-T (§232.405 of this chapter) during the preceding 12 months (or for such shorter period that the Registrant was required to submit such files). YES ☒ NO ☐

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

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

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

Indicate by check mark whether the registrant has filed a report on and attestation to its management's assessment of the effectiveness of its internal control over financial reporting under Section 404(b) of the Sarbanes-Oxley Act (15 U.S.C. 7262(b)) by the registered public accounting firm that prepared or issued its audit report. ☐

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 $345.0 million, based on the closing price of the registrant's common stock on the Nasdaq Global Select Market of $5.28 per share.

The number of shares of Registrant's Common Stock outstanding as of March 10, 2021, was 73,317,051.

DOCUMENTS INCORPORATED BY REFERENCE

The Registrant's Definitive Proxy Statement relating to the 2021 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 portions of such 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, 2020, 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," "should," "will," "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 bio-pharmaceutical company focused on fighting cancer and other life-threatening diseases by discovering and developing novel small molecule drugs that target cellular metabolism. 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 created fundamentally new potential therapies for cancer patients. With our unique approach, we have established a broad pipeline of small molecule drug candidates that target enzymes controlling metabolically critical pathways in tumor cells and immune cells. We have multiple internally discovered clinical stage compounds that are all enzyme inhibitors. While we are primarily focused on oncology, we are opportunistically developing therapeutics outside of oncology where we can leverage our existing expertise in immune cell metabolism to treat diseases with unmet need.

Through genetic mutations that alter fundamental metabolic pathways, cancer cells can acquire the ability to grow in an uncontrolled manner, but they also acquire nutrient dependencies that can differentiate them from normal cells. Targeting these nutrient dependencies by inhibiting specific metabolic pathways in cancer cells is a novel therapeutic approach to blocking the uncontrolled growth of tumors. Our lead product candidate, telaglenastat or CB-839, takes advantage of the critical dependency many cancers have on the nutrient glutamine for growth and survival. We believe telaglenastat 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 first selective allosteric glutaminase inhibitor to enter clinical trials. We retain all commercial rights to telaglenastat and have been granted a U.S. patent, which includes composition of matter coverage for telaglenastat through 2037 in the U.S. and 2032 outside of the U.S.

We are currently developing telaglenastat in combination with standard therapies in a select set of solid tumors. Our lead development pathway for telaglenastat is for the treatment of KEAP1 or NRF2 mutated non-small cell lung cancer, or NSCLC. According to third-party market research, U.S. incidence of NSCLC is 192,208 with 20% of these patients harboring KEAP1 or NRF2 activating mutations. Recently presented clinical data evaluating front-line standard-of-care chemoimmunotherapy treatment for NSCLC patients with mutations in KEAP1/NRF2 demonstrated inferior clinical outcomes compared to patients without these mutations. Thus, NSCLC patients with KEAP1 or NRF2 mutations are a population with an unmet clinical need. Pre-clinical studies have shown that activation of the KEAP1/NRF2 pathway in lung tumors makes them dependent on glutaminase activity for growth and survival, and treatment with teleglenastat selectively blocks their growth. In September 2020, we treated the first patient in the KEAPSAKE study, which is a randomized Phase 2 clinical trial of the glutaminase inhibitor telaglenastat in combination with standard-of-care therapy. The KEAPSAKE study will evaluate the safety and anti-tumor activity of telaglenastat plus standard-of-care chemoimmunotherapy as front-line treatment for patients with stage IV non-squamous non-small cell lung cancer whose tumors have a KEAP1 or NRF2 mutation determined by next-generation sequencing. The double-blind telaglenastat trial will enroll approximately 120 patients with stage IV non-squamous NSCLC with the KEAP1 or NRF2 mutation. Patients will be randomized to receive telaglenastat or placebo, in combination with pembrolizumab, carboplatin and pemetrexed. The study will evaluate the safety and investigator assessed progression-free survival, or PFS, of telaglenastat plus this standard of care chemoimmunotherapy regimen. We anticipate sharing interim data from the KEAPSAKE trial in the second half of 2021.

We were previously developing telaglenastat for the treatment of renal cell carcinoma, or RCC. In January 2021, we announced the results of the CANTATA trial, a 444 patient global, randomized, double-blind trial designed to evaluate the safety and efficacy of telaglenastat in combination with cabozantinib versus placebo with cabozantinib in patients with advanced clear cell RCC who have been treated with one or two prior lines of systemic therapy. The trial did not meet the primary endpoint of progression-free survival, or PFS. Based on this result, we evaluated our operational and workforce needs to extend our cash runway and ensure long-term sustainability. We reduced our workforce by approximately 35% to preserve cash resources. We currently have no plans to further develop telaglenastat in RCC.

As part of our Pfizer clinical collaboration, we initiated a trial with the CDK 4/6 inhibitor IBRANCE®, in combination with telaglenastat in July 2019. The Phase 1/2 trial (NCT03965845) of the combination of telaglenastat plus Ibrance is ongoing in patients with KRAS mutated colorectal cancer and KRAS mutated non-small cell lung cancer. Encouraging efficacy and safety of the combination was observed in PDAC patients treated in the dose escalation phase of the trial. In November 2020, we announced the expansion of the study to include an additional cohort of patients with pancreatic ductal adenocarcinoma whose tumors harbor mutations in both KRAS and CDKN2A. Approximately 50 percent of PDAC patients harbor mutations in both KRAS and CDKN2A.

Our product candidate, CB-280, is an oral inhibitor of arginase, an enzyme that depletes the amino acid arginine. It is being developed for the treatment of cystic fibrosis, or CF. Arginase depletes arginine, which is critical for the generation of NO, or nitric oxide. NO has critical anti-microbial effects in lung and also mediates bronchodilation. CB-280 is a novel oral arginase inhibitor

which is solely owned by Calithera. We completed a Phase 1 Single Ascending Dose trial to evaluate the safety, tolerability and pharmacokinetic profile of oral CB-280 in healthy volunteers. In July 2020, we initiated a Phase 1b clinical trial in adult patients with cystic fibrosis and chronic airway infection. The randomized, double blind, placebo-controlled, dose escalation trial will evaluate multiple ascending doses of CB-280, dosed orally twice daily for 14 days, compared to placebo in up to 32 adult CF patients to determine a safe dose range for CB-280. Enrollment in this study is ongoing and we expect to share interim data in the second half of 2021.

An additional arginase inhibitor, INCB001158, was discovered by Calithera and is being developed by Incyte Corporation, or Incyte, for oncology and hematology indications, and is currently being evaluated in Phase 1/2 trials as a monotherapy and in combination with other anti-cancer agents.

We are a fully integrated biopharmaceutical company with expertise in biology and chemistry, and our ongoing research efforts are focused on discovering additional product candidates for the treatment of cancer and other life-threatening diseases. We have discovered the clinical candidate CB-708, a potent, selective, orally administered small molecule that inhibits CD73, an enzyme that converts adenosine monophosphate to generate the immunosuppressive agent adenosine.

We have also identified CB-668, an investigational first-in-class, potent, orally administered IL4I1 inhibitor as a novel immuno-oncology approach to cancer. IL4I1 is expressed by tumor cells and antigen presenting cells and metabolizes phenylalanine, tyrosine and tryptophan to produce hydrogen peroxide, an inhibitor of T-cell function, and kynurenic acid an immunosuppressive metabolite. In syngeneic mouse models CB-668 exhibited immune mediated, single agent activity and augmented activity in combination with checkpoint inhibitors. IL4I1 expression has been correlated with poor clinical outcomes and expression is elevated in multiple tumor types including ovarian and B-cell tumors.

Our Strategy

Our goal is to be the leader in the discovery, development and commercialization of novel small molecule drugs to address unmet medical needs resulting from diseases affecting tumor and immune cell biology. Leveraging the potentially broad applicability of our tumor and immune metabolism expertise, our primary focus is in oncology, though we are opportunistically developing therapeutics outside of oncology where we can utilize existing expertise to treat diseases with unmet needs. The key elements of our strategy are to:

- **Develop telaglenastat for the treatment of NRF2/KEAP1 mutated tumors including non-small cell lung cancer, or NSCLC.** The NRF2/KEAP1 pathway is known to drive the development of certain cancers, including 20-25% of NSCLC, through the regulation of reactive oxygen species, or ROS, in a manner that requires glutaminase activity. Recently presented clinical data evaluating front-line standard-of-care chemoimmunotherapy treatment in NSCLC patients with mutations in KEAP1/NRF2 demonstrated inferior clinical outcomes compared to patient without these mutations. Multiple in vivo preclinical models have demonstrated that activation of this pathway accelerates tumor formation and growth. In addition to making tumor models more aggressive, the activation of the NRF2/KEAP1 pathway in these models also makes them very sensitive to the inhibition of glutaminase activity by telaglenastat, or CB-839. The clear mechanistic rationale, strong preclinical data, and high unmet medical need in the NSCLC population have motivated a clinical study that is evaluating telaglenastat, in combination with standard of care chemo-immunotherapy in front line NSCLC patients with tumors that harbor mutations in either KEAP1 or NRF2 that activate this pathway. We anticipate sharing interim data from the KEAPSAKE trial in the second half of 2021.

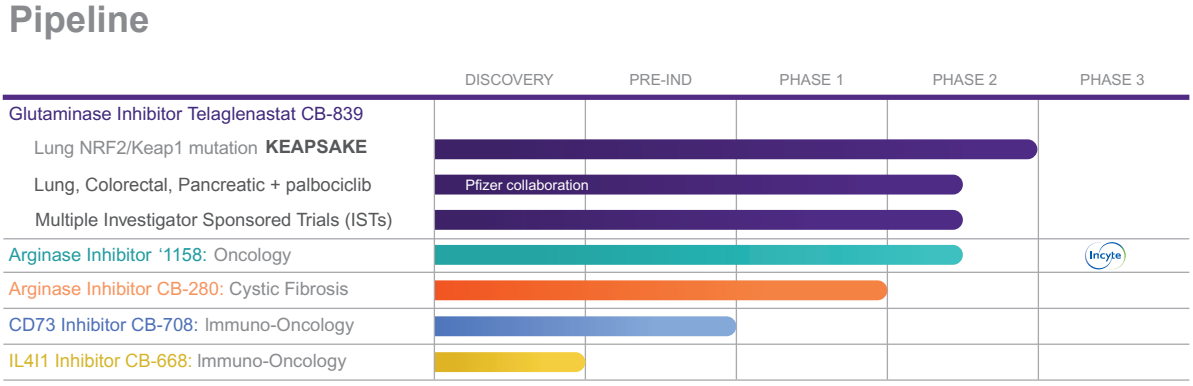
- **Advance the clinical development of telaglenastat for the treatment of additional cancers.** Mutated oncogenes can make cancer cells dependent on glutamine for growth and survival and glutaminase inhibitors have synergistic effects when combined with many cancer drugs. Through the use of clinical collaborations, National Cancer Institute and investigator-sponsored exploratory studies, we are developing telaglenastat for additional oncology indications. We have a clinical collaboration with Pfizer to evaluate Pfizer's CDK4/6 inhibitor palbociclib, also known as IBRANCE®, in combination with telaglenastat.

- **Advance the clinical development of CB-280 as a new treatment modality for cystic fibrosis, or CF.** Arginase and the amino acid arginine are believed to be critical in the pathology of cystic fibrosis. Neutrophils accumulate in the lungs of CF patients and secrete arginase, an enzyme that metabolizes arginine and impairs production of nitric oxide, while generating arginine metabolites that may impair lung function. CB-280 is an orally administered small molecule inhibitor of arginase. We are enrolling a Phase 1b trial to evaluate the safety, tolerability and pharmacokinetic profile of oral CB-280 in cystic fibrosis patients and we expect to share interim data in the second half of 2021.

- **Apply our insights in tumor metabolism and immuno-oncology to discover and develop additional targets beyond our current clinical pipeline.** Our research focus has remained on metabolic enzymes, but our portfolio has diversified into the therapeutic areas of oncology, immuno-oncology and cystic fibrosis. We have two earlier stage immunotherapy programs which include our clinical candidate CB-708, which targets CD73, an enzyme in the tumor microenvironment that produces the immuno-suppressive metabolite adenosine, as well an IL4I1 inhibitor program.

Our Research and Development Programs

The following table summarizes our ongoing and planned clinical trials for our lead programs. 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. Emerging 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. 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 less 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.

Rewired metabolic signaling pathways are a hallmark of many cancers. Targeting oncometabolism is a novel therapeutic approach to blocking cancer growth. Many cancer cells excessively consume nutrients, such as glutamine and glucose, to meet increased metabolic demands. Glutamine is a critical fuel for the metabolic demands of cancer cell growth. Glutaminase catalyzes the conversion of glutamine to glutamate and is frequently overexpressed in cancer. Cancer cells can become dependent on glutaminase in response to oncogene signaling and thus glutaminase is emerging as a novel target for cancer therapeutics.

Our Programs

Our Glutaminase Inhibitor Telaglenastat (CB-839)

Our lead product candidate, telaglenastat, takes advantage of the pronounced dependency many cancers have on the nutrient glutamine for growth and survival. Telaglenastat is a novel, selective glutaminase inhibitor that blocks glutamine consumption in tumor cells and demonstrates synergistic antitumor effects with multiple anticancer therapies in preclinical studies.

Inhibition of glutaminase prevents glutamine from serving its critical roles in nucleic acid synthesis, DNA repair, cell cycle progression, energy generation, and protection from oxidative stress. Telaglenastat produces synergistic anti-tumor effects in preclinical studies when used in combination with multiple classes of anti-cancer therapies. Because telaglenastat has multiple mechanisms for impacting cellular metabolism, it has anti-tumor effects on a number of different tumor types when combined with a variety of different agents, including tyrosine kinase inhibitors, mTOR inhibitors, chemotherapeutic agents (such as platinum agents and taxanes), immune checkpoint inhibitors, CDK4/6 inhibitors and PARP inhibitors.

Telaglenastat binds to a site on glutaminase distinct from the glutamine-binding active site, making it a highly selective and unique allosteric inhibitor. Telaglenastat is well-tolerated in part because of this selectivity. We believe telaglenastat 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 first selective allosteric glutaminase inhibitor currently in clinical trials. We retain all commercial rights to telaglenastat and have been granted a U.S. patent, which provides composition of matter coverage for telaglenastat through 2037, as well as patents applied for/issued in other territories.

In February 2014, we initiated three Phase 1 clinical trials to assess the safety and tolerability of telaglenastat in patients with solid and hematological tumors. Most patients in these trials were relapsed and refractory to multiple approved therapies. These studies showed that drug concentration generally increases with dose, and increasing concentration of telaglenastat in blood correlates with increasing inhibition of glutaminase in blood platelets and tumors. The half-life of telaglenastat in blood is approximately four hours. We have observed this dosing regimen provides sufficient glutaminase inhibition at steady state dosing and the average exposure is above levels we are targeting. Telaglenastat is dosed with food on a twice-daily regimen.

Telaglenastat has been generally well-tolerated using doses up to 1000 mg administered either twice or three times daily. The primary reported treatment-related toxicities with monotherapy telaglenastat observed to date include fatigue, gastrointestinal events (nausea, vomiting, and constipation), elevations in liver function tests, or LFTs, and photophobia. The majority of these adverse events have been mild to moderate (Grade 1/2) in severity.

Evaluation of telaglenastat in combination in non-small cell lung cancer (NSCLC) with NRF2/KEAP1 pathway mutations

Effective treatments for patients with KEAP1 or NRF2 mutations remain a large unmet clinical need. According to third-party market research, U.S. incidence of NSCLC is 192,208. Activating mutations in the KEAP1/NRF2 pathway, which occur in an estimated 20 percent of non-squamous NSCLC patients, occur early in tumor development and drive aggressive tumor growth. Recently presented clinical data demonstrate that activation of this pathway through the loss of KEAP1 function results in very poor outcomes in NSCLC patients receiving front line standard of care chemotherapy or chemo-immunotherapy. In a recently published observational study (Skoulidis, ASCO 2019) the survival of patients with KEAP1 genomic alterations treated with standard-of care first line chemo-immunotherapy was statistically significantly shorter when compared to patients without the mutations (7.8 months vs. 20.4 months p=0.002).

Proliferating tumors are metabolically active and can accumulate high levels of reactive oxygen species (ROS). Activation of the NRF2/KEAP1 pathway induces the expression of many genes that allow the tumor to better manage these high levels of ROS. A key subset of these activated genes regulate the uptake and metabolism of glutamine and the synthesis of glutathione, making tumors that harbor these mutations dependent on the activity of glutaminase. Multiple in vivo preclinical models have demonstrated that activation of this pathway, through loss of KEAP1 function or a gain-of-function NRF2 mutation, accelerates tumor formation and spread. In addition to making tumor models more aggressive, the activation of the NRF2/KEAP1 pathway in these models also makes them very sensitive to the inhibition of glutaminase activity by telaglenastat. Genetic analysis of adenocarcinoma NSCLC tumors from patients indicate that NRF2/KEAP1 mutations occur early in tumor development. The clear mechanistic rationale, strong preclinical

data, and high unmet medical need in the NSCLC population have motivated a randomized clinical study that will evaluate telaglenastat, in combination with standard of care chemo-immunotherapy in front line NSCLC patients with tumors that harbor mutations in either KEAP1 or NRF2 that activate this pathway.

In September 2020, we treated the first patient in the KEAPSAKE (NCT04265534) study, which is a randomized Phase 2 clinical trial of the glutaminase inhibitor telaglenastat in combination with standard-of-care therapy. The KEAPSAKE study will evaluate the safety and anti-tumor activity of telaglenastat plus standard-of-care chemoimmunotherapy as front-line treatment for patients with stage IV non-squamous non-small cell lung cancer whose tumors have a KEAP1 or NRF2 mutation determined by next-generation sequencing. The double-blind telaglenastat trial will enroll approximately 120 patients with stage IV non-squamous NSCLC with the KEAP1 or NRF2 mutation. Patients will be randomized to receive telaglenastat or placebo, in combination with pembrolizumab, carboplatin and pemetrexed. Patients are stratified by STK11/LKB1 mutational status and the M stage of cancer (M1a-b vs. M1c). The study will evaluate the safety and investigator assessed progression-free survival, or PFS, of telaglenastat plus this standard of care chemoimmunotherapy regimen. Guardant360 liquid biopsy test will be provided by the study sponsor as an investigational use only, or IUO, testing option for patient selection. We anticipate sharing interim data from the KEAPSAKE trial in the second half of 2021.

Evaluation of telaglenastat in renal cell carcinoma (RCC)

Telaglenastat has been evaluated in two randomized trials for the treatment of RCC, but is not currently being developed for this indication. RCC commonly exhibits genetically-driven metabolic alterations that increase their dependence on glutamine, which creates opportunities to develop novel agents targeting glutamine metabolism that could improve patient outcomes. In January 2021, we reported the topline results of the CANTATA trial. The CANTATA trial (NCT03428217) was a global, randomized, double-blind trial designed to evaluate the efficacy and safety of telaglenastat in combination with cabozantinib versus placebo with cabozantinib in patients with advanced or metastatic RCC who have been treated with one or two prior lines of systemic therapy, including at least one vascular endothelial growth factor, or VEGF-pathway targeted anti-angiogenic therapy, or the combination of nivolumab and ipilimumab. The CANTATA trial enrolled 444 patients at multiple centers globally. Exelixis, Inc. provided cabozantinib for the trial through a material supply agreement with Calithera. As compared to treatment with cabozantinib, the combination of telaglenastat and cabozantinib did not meet the primary endpoint of improving progression free survival, or PFS, in the study population. The primary study endpoint is PFS by blinded independent review. The hazard ratio was 0.94 (p=0.65). Median PFS was 9.2 months among patients treated with telaglenastat and cabozantinib as compared to 9.3 months with cabozantinib and placebo. Sixty-two percent of patients were treated with prior PD(L)-1 containing therapy, and the arms were well balanced. The frequency and severity of adverse events in the telaglenastat-treated population were comparable to that of cabozantinib alone. We have submitted the results for presentation at a medical meeting.

The ENTRATA trial (NCT03163667) was a Phase 2 randomized, double blind trial designed to evaluate the safety and efficacy of telaglenastat in combination with everolimus versus placebo with everolimus in patients with advanced clear cell RCC who have been treated with at least two prior lines of systemic therapy, including at least one VEGFR-targeted tyrosine kinase inhibitor, or TKI. Patients were randomized in a 2:1 ratio. The trial opened for enrollment in August 2017 and completed enrollment in January 2019. The trial enrolled 69 patients at multiple centers in the United States and results were presented earlier this year. Key demographics were balanced between the two treatment arms. Patients enrolled were heavily pre-treated with a median of three prior lines of therapy for advanced metastatic disease including 70% (72% vs. 65% in telaglenastat and placebo arms, respectively) with two or more prior TKIs, and 68% (70% vs. 65%) with intermediate/poor MSKCC prognostic score. Eighty-eight percent of patients received prior PD-1/PD-L1 therapy (91% vs. 83%). Telaglenastat, when added to everolimus, doubled the median PFS to 3.8 months as compared to 1.9 months for everolimus alone and reduced the risk of disease progression or death by 36% (HR=0.64, p=0.079 one-sided). The primary endpoint of the trial was PFS per investigator assessment with a predetermined threshold of $p \leq 0.2$ one-sided. Overall response per Response Evaluation Criteria in Solid Tumors version 1.1 (RECIST v.1.1) was 2.2% vs. 0%, and stable disease was 56.5% vs. 47.8%. Based on a data cutoff of September 30, 2020, the median overall survival is 14.4 months vs. 9.7 months in the telaglenastat and control arms, respectively (HR=0.80, p=0.24 one-sided).

Frequency of all-grade adverse events in the telaglenastat-containing arm were comparable to that of everolimus alone. Grade 3 or higher adverse events occurred in 80.4% of patients in the telaglenastat plus everolimus arm versus 60.9% in the everolimus plus placebo arm. The most frequently reported Grade ≥ 3 adverse events in the treatment versus control arms, respectively, were anemia (17.4% vs. 17.4%), pneumonia (6.5% vs. 4.3%), abdominal pain (6.5% vs. 0%), thrombocytopenia (6.5% vs. 0%), and fatigue (4.3% vs. 8.7%). Adverse events leading to discontinuation of any study drug were comparable (28.3% vs. 30.4%).

Evaluation of telaglenastat in combination with palbociclib (Ibrance)

In October 2018, we announced a collaboration with Pfizer to evaluate the CDK4/6 inhibitor palbociclib (Ibrance) in combination with telaglenastat for the treatment of patients with KRAS mutated colorectal cancer and patients with KRAS mutated

non-small cell lung cancer. Preclinical data suggest that telaglenastat, which is designed to starve tumor cells of the key nutrient glutamine, synergizes with CDK4/6 inhibitors by enhancing cell cycle arrest and blocking cancer cell proliferation. The combination of telaglenastat with CDK4/6 inhibitors has demonstrated synergistic activity in a number of preclinical cancer models, including colorectal cancer, or CRC, non-small cell lung carcinoma, or NSCLC, triple negative breast cancer, or TNBC, and ER+ breast cancer. Based on these data, we initiated a Phase 1/2 clinical trial of the combination of telaglenastat plus palbociclib in patients with KRAS mutated CRC and patients with KRAS mutated NSCLC in July 2019. The Phase 1/2 trial (NCT03965845) of the combination of telaglenastat plus Ibrance has been evaluating patients with KRAS mutated colorectal cancer and KRAS mutated non-small cell lung cancer. In the ongoing trial, encouraging efficacy and safety of the combination was observed in PDAC patients treated in the dose escalation phase of the trial. In November 2020, we announced the expansion of the study to include an additional cohort of patients with pancreatic ductal adenocarcinoma whose tumors harbor mutations in both KRAS and CDKN2A. Approximately 50 percent of PDAC patients harbor mutations in both KRAS and CDKN2A. In preclinical studies with KRAS-mutated cancer models, telaglenastat showed synergistic anti-tumor effects when used in combination with CDK4/6 inhibitors, such as palbociclib, enhancing cell cycle arrest and blocking cancer cell proliferation.

Evaluation of telaglenastat in additional indications

Telaglenastat is also the subject of several additional investigator-sponsored clinical trials and is available under the NIH/NCI Cancer Therapy Evaluation Program, or CTEP, collaborative agreement for clinical and non-clinical studies. Investigator-sponsored Phase 2 trials are ongoing and recruiting patients with PIK3CA mutant CRC, RAS wild-type CRC and myelosdysplastic syndrome, or MDS. A clinical trial in patients with PIK3CA mutant CRC is ongoing at Case Western and Cleveland Clinic. This research is supported by a Stand Up To Cancer Colorectal Cancer Dream Team Translational Research Grant (Grant Number: SU2C-AACR-DT22-17). As of the June 2018 data presentation, 16 patients have been enrolled, including 12 patients with CRC. CRC patients must have progressed on prior fluoropyrimidine-containing therapy. In the dose escalation phase of the trial, there were no dose limiting toxicities and telaglenastat plus capecitabine was well tolerated at the full dose of telaglenastat. All late-line CRC patients had progressed on at least one prior fluoropyrimidine-containing regimen. For CRC patients with PIK3CA-mutated cancer (n=7), the median PFS was 26 weeks and for patients with PIK3CA wild-type cancer (n=5) the median PFS was 16 weeks (p=0.058). These results compare favorably to historical data in third line CRC patients receiving standard of care therapies, where the median PFS is approximately 8 weeks. The Phase 2 dose expansion portion of this study in patients with PIK3CA mutant colorectal cancer is ongoing. Additional investigator sponsored trials include the following:

- A clinical trial in patients with KRAS wild-type CRC is ongoing at Vanderbilt evaluating telaglenastat plus panitumumab in anti-EGFR-refractory patients. Dose escalation is complete and the Phase 2 portion of this trial is ongoing.
- A clinical trial in patients with high risk MDS is ongoing at MD Anderson Cancer Center. Phase 2 is ongoing and an interim analysis was presented at the 2020 American Society of Hematology Annual meeting. As of the data cutoff of July 2020, 23 patients had been enrolled and 6 patients remained on study.
- A clinical trial in patients with platinum resistant BRCA wild-type ovarian cancer is ongoing at the University of Alabama at Birmingham evaluating teleglenastat plus niraparib.

In addition to the investigator sponsored trials, a total of five NIH/NCI CTEP trials are ongoing. These trials include the following:

- A study of telaglenastat in combination with carfilzomib and dexamethasone for the treatment of multiple myeloma
- A study of telaglenastat plus radiation therapy and temozolomide in patients with IDH mutant glioma
- A study of telaglenastat plus osimertinib in patients with EGFR mutant NSCLC
- A study of telaglenastat monotherapy in patients with solid tumors with NF1, KEAP1/NRF2 or STK11 mutations
- A study of telaglenastat plus sapanisertib in patients with advanced NSCLC with KEAP1/NRF2/STK11 mutations

Preclinical Activity of Telaglenastat

Telaglenastat is a novel, selective glutaminase inhibitor that blocks glutamine consumption in tumor cells and demonstrates synergistic antitumor effects with multiple anticancer therapies in preclinical studies. Telaglenastat targets an allosteric binding site that is highly specific for glutaminase. Inhibition of glutaminase prevents glutamine from serving its critical roles in nucleic acid synthesis, DNA repair, cell cycle progression, energy generation, and protection from oxidative stress. Single-agent telaglenastat blocks growth and survival in glutamine-dependent cancer cell lines and tumor xenograft models.

At plasma concentrations of telaglenastat 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 telaglenastat. 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 telaglenastat are well tolerated in animals.

Inhibition of glutaminase also results in the reduction of the antioxidant molecule glutathione. The master transcriptional regulator NRF2 induces more than 200 genes related to antioxidant stress including genes responsible for glutathione biosynthesis. Somatic mutations in the NRF2/KEAP1 pathway are present in lung cancers, head and neck cancers, hepatocellular carcinoma and other cancer types. Lung cancer models with NRF2/KEAP1 pathway mutations showed marked sensitivity to inhibition by telaglenastat which is believed to be due to pronounced dependence on tumor cell glutathione production that is blocked by glutaminase inhibition.

Telaglenastat produces synergistic antitumor effects in preclinical studies when used in combination with multiple classes of standard-of-care anticancer therapies. Telaglenastat 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. Telaglenastat was synergistic with the epidermal growth factor receptor, or EGFR, inhibitor erlotinib (marketed as Tarceva®) in non-small cell lung cancer, or 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 RCC, cells. We believe these synergistic activities likely result from the fact that growth factor pathways also control tumor metabolism and ultimately tumor cell dependence on glutamine and glucose.

Glutaminase inhibition blocks the formation of key metabolic intermediates needed for nucleotide synthesis in cancer cells and enhances the activity of DNA synthesis blocking agents, such as CDK4/6 inhibitors, and DNA repair inhibitors, such as PARP inhibitors. Telaglenastat is synergistic with the CDK4/6 inhibitor palbociclib in ER+, estrogen-resistant breast cancer lines, which results from enhanced cell cycle blockade. Furthermore, telaglenastat was recently shown to induce double-strand DNA breaks in tumor cells and had synergistic activity *in vitro* and *in vivo* in RCC cell lines with the PARP inhibitor olaparib (marketed as Lynparza®).

In preclinical models, telaglenastat enhances the antitumor activity of immune checkpoint inhibitors by relieving nutrient competition in the tumor microenvironment, which potentially supports T-cell function. Telaglenastat also acted synergistically when combined with I-O drugs that inhibited the PD-1/PD-L1 immune cell checkpoint. 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 telaglenastat by the increased availability of glutamine in the tumor microenvironment. Telaglenastat 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. Similar activity was observed when an anti-PD-L1 checkpoint inhibitor was used in combination with telaglenastat. Anti PD-1 is known to increase glucose utilization in T-cells, and we believe that telaglenastat, 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 IND-enabling toxicity studies, telaglenastat was well tolerated, with no dose limiting toxicities observed. The plasma concentration of telaglenastat 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, telaglenastat 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.

Arginase Inhibitor CB-280

Arginase has been proposed to be critical in the pathophysiology of several non-oncology diseases, including cystic fibrosis, or CF. CF patients have a mutation in the gene that encodes the cystic fibrosis transmembrane-conductance regulator, or CFTR, making them particularly susceptible to progressive loss in lung function. Airway disease in CF has a complex pathophysiology and, despite recent advances in developing therapies for CF, there still remains an unmet need. CB-280 is a potent and selective oral inhibitor of arginase. Neutrophils accumulate in the lungs of CF patients and secrete arginase. Sputum from patients with CF has elevated arginase activity leading to diminished arginine levels. Reduced arginine is thought to exacerbate pulmonary disease in CF by impairing production of nitric oxide, leading to a diminished anti-microbial response and impaired airway function. It is known that airways of patients with CF have lower than normal nitric oxide, or NO, production, and lower NO levels directly correlate with worsened lung

function and increased colonization with pathogens, including Pseudomonas aeruginosa. Research in CF patients has demonstrated that increasing arginine levels can increase the production of nitric oxide and improve lung function. In addition, published preclinical data also demonstrated that arginine-dependent NO-based signaling was associated with increased function of the CFTR (Wu et al. Molecular Pharmacology 2019). The result was that the use of an arginase inhibitor improved the function of delta 508 mutant CFTR in the presence or absence of a CFTR modulator as demonstrated by a change FLIPR fluorescence from baseline.

We, along with our pre-clinical collaborators, have validated arginase inhibitors in mouse models of CF. In October 2020, we presented a trial in progress poster detailing the trial design at the North American Cystic Fibrosis 2020 Virtual Conference. The poster presentation includes preclinical study results which suggest CB-280 significantly improved lung function and reduced Pseudomonas aeruginosa colony-forming units in pre-clinical models. Arginase inhibition with CB-280 resulted in improved central airway resistance in CFTR knockout mice, and decreased lung infection in wild type and DeltaF508-CFTR-expressing mice infected with Pseudomonas. Based on pre-clinical studies in a mouse model of CFTR-mutated CF, we believe that arginase inhibition can lead to reduced infection and improved lung function in CF patients and that these data support the clinical development of CB-280 in CF. In February 2019, we initiated a Phase 1 trial conducted under an IND application. The first-in-human Phase 1 Single Ascending Dose trial, which is now complete, evaluated the safety, tolerability and pharmacokinetic profile of oral CB-280 in healthy volunteers. A Phase 1b clinical study in CF patients was initiated in July 2020, evaluating multiple doses of CB-280 compared to placebo in 32 adult CF patients to determine a maximum tolerated dose, or MTD, range for CB-280 in CF patients. Patients at study entry must be stable on CF background therapies with FEV1 40-90% of predicted. Patients will receive CB-280 or placebo for 14 days; lung function as well as microbes in sputum will be evaluated. A dose-finding expansion of this study is planned in which additional cohorts of patients will receive different doses of CB-280 or placebo for 28 days in order to select the optimal dose of CB-280 to improve lung function. For the entire study, patients will continue their existing therapies for CF (including CFTR modulators).

In November 2020, we were awarded up to $2.4 million from the Cystic Fibrosis Foundation.

Under our collaboration agreement with Incyte, we retained the sole right to develop and commercialize CB-280 in specific non-oncology rare disease indications, including CF. Arginase is also thought to play an important pathophysiologic role in several other diseases, including idiopathic pulmonary fibrosis and other fibrotic diseases, primary pulmonary hypertension, acute respiratory distress syndrome, and others.

Arginase Inhibitor INCB001158

Immune surveillance is the process whereby the body identifies pathogens as well as abnormal cells that are either infected with viruses or have become cancerous. Upon recognition of foreign or abnormal cells, a number of immune processes are activated to allow the body to attack and clear cells. However, excessive or inappropriate activation of the immune system can have negative consequences such as autoimmune disease, inflammation, or maternal-fetal rejection. Compensatory mechanisms have evolved to control excessive inflammatory activity by dampening the immune stimulation. Cancerous cells that successfully evade immune surveillance do so, in part, by blocking or reducing immune-stimulatory and/or enhancing immune-inhibitory activities. Immuno-oncology therapies interfere with mechanisms that tumors have used to dampen the immune response.

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 reported in many solid tumor types including lung cancer, 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 cancers and bladder cancers. 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.

INCB001158, a potent and selective orally bioavailable inhibitor of the enzyme arginase, was discovered by us and is being developed with Incyte. 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, squamous cell cancer of the head and neck, 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. INCB001158 entered clinical trials in September 2016 and is currently being tested in four ongoing clinical trials. The first Phase 1b/2 trial (NCT02903914) is designed to evaluate the safety and recommended Phase 2 dose of INCB001158 as a mono-therapy and in combination with the immune checkpoint inhibitor pembrolizumab.

A second clinical trial (NCT03314935) designed to evaluate INCB001158 in combination with chemotherapy opened for enrollment in November 2017. The Phase 1/2 trial in patients with solid tumors (including metastatic microsatellite stable colorectal cancer, biliary tract cancer, gastroesophageal cancer, endometrial cancer or ovarian cancer), is evaluating INCB001158 administered orally twice daily with either FOLFOX, gemcitabine/cisplatin or paclitaxel. Primary endpoints include safety and objective response rate.

Two additional Phase 1/2 trials are ongoing. One is evaluating the safety and anti-tumor activity of INCB001158 in combination with daratumumab compared to daratumumab alone in refractory multiple myeloma patients (NCT03837509). The other is evaluating the safety and pharmacokinetics of INCB001158 alone and in combination with INCMGA00012, an experimental PD-1 inhibitor (NCT03910530).

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 co-develop and co-commercialize our small molecule arginase inhibitors for hematology and oncology indications. In April 2020, we filed a complaint against Incyte in the Superior Court of California, San Francisco County, asserting claims for breach of contract arising out of Incyte's failure to pay two milestone payments we believe are due under the Collaboration and License Agreement between us and Incyte, or the Incyte Collaboration Agreement. While we remain committed to and confident in the INCB001158 development program, we have decided to opt out of our co-development obligations at this time effective September 30, 2020, as permitted under the terms of the Incyte Agreement, in order to focus our resources on our own internal development programs. As a result of our decision to opt out, Incyte will pay all costs to develop INCB001158 or any other licensed products. In addition, our rights to U.S. profit sharing will no longer be in effect, and instead Incyte will pay us tiered royalties ranging from the low double digits to mid-teens on net sales of licensed products in the U.S., additional royalties to reimburse us for previously incurred development costs, and total remaining potential development, regulatory and commercialization milestones of $738.0 million (increased from over $418.0 million prior to the opt out). Our rights to royalties outside the U.S. remain unchanged. We will also have no further rights to research, develop or co-detail INCB001158 and Incyte will have the right to take over the conduct of all activities related to the research, development and commercialization of INCB001158 for all indications in the hematology/oncology field.

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 License 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.

Early Immuno-Oncology Programs

Our research focus has remained on metabolic enzymes. We have two earlier stage immunotherapy programs which include our candidate CB-708, which targets CD73, an enzyme in the tumor microenvironment, as well an IL4I1 inhibitor program.

CD73 is an enzyme that produces adenosine, a powerful inhibitor of immune function in tumors. CD73 is expressed across a wide range of tumors and tumor infiltrating leukocytes, and often correlates with poor prognosis. Blockade of adenosine production by CD73 inhibition is expected to reverse immunosuppression in the tumor microenvironment and enhance the immune system's ability to fight the cancer. We have developed an orally-bioavailable small molecule inhibitor of CD73, CB-708, that has anti-tumor activity in mouse syngeneic models both as monotherapy and in combination with checkpoint inhibitors as well as chemotherapy. Preclinical data were presented at the 2019 American Association for Cancer Research annual meeting in April and the Society for Immunotherapy of Cancer meeting in November demonstrating that CB-708 is a potent and selective inhibitor of CD73 that has immune-mediated, single agent activity in syngeneic mouse tumor models. In pre-clinical studies CB-708 was well-tolerated and shows enhanced anti-tumor activity when combined with either an anti-PD-L1 immunotherapy or with chemotherapeutic agents, such

as oxaliplatin or doxorubicin. Despite the promising preclinical data on CB-708, we have chosen to de-prioritized development of this program at this time and we do not have any current plans to advance the candidate into clinical trials.

We have also identified CB-668, an investigational first-in-class, potent, orally administered IL4I1 inhibitor as a novel immuno-oncology approach to cancer. CB-668 is an inhibitor of the enzyme IL4I1, an enzyme that is expressed by tumor cells and antigen presenting cells, metabolizes phenylalanine, tyrosine and tryptophan to produce hydrogen peroxide, an inhibitor of T-cell function. In particular, IL4I1 can metabolize tryptophan to kynurenic acid and other metabolites that lead to immunosuppression in the tumor microenvironment. Preclinical data were presented at the 2020 Society for Immunotherapy of Cancer Annual Meeting. In syngeneic mouse models CB-668 exhibited immune mediated, single agent activity and augmented activity in combination with checkpoint inhibitors. IL4I1 expression has been correlated with poor clinical outcomes and expression is elevated in multiple tumor types including ovarian and B-cell tumors. We plan to begin a preclinical study in canine lymphoma patients in the second half of 2021.

Intellectual Property

Our commercial success depends in large part on our ability to obtain and maintain intellectual property protection for our product candidates, including telaglenastat, INCB001158, CB-280, 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 treating disease. We are also 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, 2020, we owned 20 issued U.S. patents, 42 issued foreign patents, and approximately 302 pending U.S. and foreign patent applications in the following foreign jurisdictions: Argentina, Australia, Brazil, Canada, Chile, China, Colombia, Costa Rica, Ecuador, the Eurasian Patent Organization, Europe, Hong Kong, Indonesia, India, Israel, Japan, Malaysia, Mexico, New Zealand, Peru, Philippines, Russia, Singapore, South Africa, South Korea, Sri Lanka, Taiwan, Thailand, Ukraine, Venezuela, and Vietnam. We expect that these patents and patent applications, if issued, would expire between April 2031 and October 2041.

As of December 31, 2020, the intellectual property portfolio for our glutaminase inhibitor program, which includes telaglenastat, included ten issued U.S. patents. Six of these U.S. patents expire between 2032 and 2037 and claim compositions of matter for and methods of treating cancer with telaglenastat. The other U.S. patents expire between 2035 and 2037, claiming methods of treating cancer with telaglenastat. We also have 36 issued foreign patents, seven pending U.S. patent applications and 97 corresponding pending PCT and foreign patent applications directed to compositions of matter for telaglenastat and related chemical compounds, as well as methods of using these compounds. This portfolio includes one granted U.S. patent and one pending U.S. patent application relating to methods for measuring 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 September 2041.

The intellectual property portfolio for our arginase inhibitor program, which includes INCB001158 and CB-280, includes issued patents and pending patent applications that we have exclusively licensed from Symbioscience as well as issued patents and pending patent applications that we own. This portfolio includes 17 issued U.S. patents, seven pending U.S. patent applications, 150 corresponding pending foreign patent applications, and 50 issued foreign patents directed to various arginase inhibitors, therapeutic methods of using the compounds, methods of making the compounds, and intermediates useful in preparing the compounds. We expect that these patents and patent applications, if issued, would expire between April 2031 and May 2038.

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 telaglenastat and CB-280. Telaglenastat and CB-280 are organic compounds of low molecular weight. Our third-party contract manufacturers are currently producing telaglenastat and CB-280 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 telaglenastat and CB-280. 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 telaglenastat and CB-280. Incyte Corporation has responsibility for manufacturing of INCB001158 drug substance and drug product.

Research and Development

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.

Coverage and Reimbursement

Significant uncertainty exists as to the coverage and reimbursement status of any drugs for which we may obtain regulatory approval. In the United States and markets in other countries, sales of any drugs for which we receive regulatory approval for commercial sale will depend in part on the availability of coverage and reimbursement from third-party payors. Third-party payors include government authorities, managed care plans, private health insurers and other organizations. The process for determining whether a third-party payor will provide coverage for a drug may be separate from the process for setting the reimbursement rate that the payor will pay for the drug. One third-party payor's decision to cover a particular drug does not ensure that other payors will also provide coverage for the drug, or will provide coverage at an adequate reimbursement rate. Adequate third-party reimbursement may not be available to enable us to maintain price levels sufficient to realize an appropriate return on our investment in drug development.

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.

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 in the fields of tumor immunology, tumor metabolism, and/or other product candidates in development for advanced cancer treatment include Agios Pharmaceuticals, Inc., Arcus Biosciences, Inc., AstraZeneca plc, Boehringer Ingelheim GmbH, Bayer Pharma AG, Bristol-Myers Squibb Company, Celgene Corporation, Corvus Pharmaceuticals, Inc., Dracen Pharmaceuticals, Inc., Eisai Co., Ltd., Eli Lilly and Company, GlaxoSmithKline plc, Incyte Corporation, iTeos Therapeutics SA, Merck & Co., Merck KGaA, Nektar Therapeutics, Novartis International AG, Pfizer Inc, Roche Holdings AG and its subsidiary Genentech, Inc., and Takeda Pharmaceutical Co., Ltd.

Our primary competitors in the field of Cystic Fibrosis include AbbVie, Inc., Beyond Air Inc., Corbus Pharmaceuticals Holdings, Inc., Novartis AG, Novoteris, LLC, Proteostatis Therapeutics, Inc., Translate Bio, Inc., and Vertex Pharmaceuticals, Inc.

The most common methods of treating patients with cancer are surgery, radiation and drug therapy, including chemotherapy, hormone therapy, targeted drug therapy, and immunotherapy. 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 may 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 telaglenastat, INCB001158, 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 implements 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 or purchase 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 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 accepted for filing. 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

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. 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. The FDA may later decide that the product candidate no longer meets the conditions for breakthrough therapy designation.

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, or 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, or 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 provides 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. Physicians, on the other hand, may prescribe products for off label uses. Although the FDA and other regulatory agencies do not regulate a physician's choice of drug treatment made in the physician's independent medical judgment, they do restrict promotional communications from companies or their sales force with respect to off label uses of products for which marketing clearance has not been issued. Companies may only share truthful and not misleading information that is otherwise consistent with a product's FDA approved labeling. 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 U.S. Healthcare Regulations

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, among others, 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. 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. Violations of the anti-kickback statute and false claims laws are punishable by imprisonment, criminal fines, civil monetary penalties, possible exclusion from participation in federal healthcare programs and integrity oversight and reporting obligations to resolve allegations of non-compliance with this law. 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.

We may also be subject to additional federal and state laws related to physician transparency, data privacy and security, and pharmaceutical manufacturer compliance guidelines, including the federal Health Insurance Portability and Accountability Act of 1996 and the Physician Payments Sunshine Act.

If our operations are found to be in violation of any of the laws described above or any other government regulations that apply to us, we may be subject to penalties, including significant administrative, civil and criminal penalties, damages, fines, additional reporting requirements and oversight if we become subject to a corporate integrity agreement or similar agreement to resolve allegations of noncompliance with these laws, exclusion from participation in government health care programs, such as Medicare and Medicaid, disgorgement, imprisonment, contractual damages, reputational harm and the curtailment or restructuring of our operations, any of which could harm our ability to operate our business and our results of operations.

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, 2020, we had 94 employees, 92 of which were full-time employees, including 26 employees with Ph.D. or M.D. degrees. Of these full-time employees, 62 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. On January 4, 2021, we announced a reduction in force by approximately 35%, which we anticipate the majority to be completed by the end of the first quarter of 2021.

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. In March 2021, we entered into an amendment to our lease where we reduced our leased space to approximately 34,000 square feet. 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.

Available Information

We were incorporated in the State of Delaware on March 9, 2010. Our website address is www.calithera.com. Information found on, or accessible through, our website is not a part of, and is not incorporated into, this Annual Report on Form 10-K.

We file electronically with the U.S. Securities and Exchange Commission, or SEC, our annual reports on Form 10-K, quarterly reports on Form 10-Q, current reports on Form 8-K, and amendments to those reports filed or furnished pursuant to Section 13(a) or 15(d) of the Securities Exchange Act of 1934, as amended. We make available on our website at *www.calithera.com*, free of charge, copies of these reports as soon as reasonably practicable after filing these reports with, or furnishing them to, the SEC.

Item 1A. Risk Factors.

Our business involves significant risks, some of which are described below. You should carefully consider these risks, in addition to the other information contained in this Annual Report on Form 10-K, including our consolidated financial statements and related notes and the section of this report titled "Management's Discussion and Analysis of Financial Condition and Results of Operations." The occurrence of any of the events or developments described in the following risk factors and the risks described elsewhere in this report 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. This report on Form 10-K also contains forward-looking statements that involve risks and uncertainties. Our actual results could differ materially from those anticipated in the forward-looking statements as a result of factors that are described in the following risk factors and the risks described elsewhere in this report.

Summary Risk Factors

Our business is subject to numerous risks and uncertainties, including those highlighted in the section titled "Risk Factors" immediately following this summary. These risks include, among others, the following:

- 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.
- 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.
- Our business, operations and clinical development plans and timelines are currently adversely affected by and could be adversely affected in the future by the effects of health epidemics, including the recent COVID-19 pandemic, on the manufacturing, clinical trial and other business activities performed by us or by third parties with whom we conduct business, including our contract manufacturers, Clinical Research Organizations, or CROs, shippers and others.
- 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 drug discovery and development efforts might not generate successful product candidates.
- 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.
- If we experience delays or difficulties in enrolling patients in clinical trials, our receipt of necessary regulatory approvals could be delayed or prevented.
- 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.
- Results of preclinical studies and early clinical trials may not be predictive of results of future clinical trials.
- We face substantial competition, which may result in others discovering, developing or commercializing products before or more successfully than we do.
- Product liability lawsuits against us could cause us to incur substantial liabilities and could limit the commercialization of any product candidates we may develop.
- 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 rely on third parties to conduct our clinical trials and some aspects of our research and preclinical testing and manufacture our product candidates, and those third parties may not perform satisfactorily, including failing to meet deadlines for the completion of such trials, research or testing.
- Our arginase inhibitors program in hematology and oncology indications, including INCB001158, is reliant in part on Incyte for the successful development and commercialization in a timely manner. If Incyte does not devote sufficient resources to INCB001158'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 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 internal computer systems, or those used by our Clinical Research Organizations or other contractors or consultants, may fail or suffer security breaches.
- If we are alleged to infringe intellectual property rights of third parties, our business could be harmed.
- We may not be able to protect, or fully exploit, our intellectual property rights throughout the world, which could impair our competitive position.
- 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.

- 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.
- Our future success depends on our ability to retain our senior management team and to attract, retain and motivate qualified personnel.
- The trading price of our common stock is likely to be volatile, and purchasers of our common stock could incur substantial losses.
- If we are unable to maintain proper and effective internal controls over financial reporting, the accuracy and timeliness of our financial reporting and the market price of our common stock may be adversely affected.
- If we are unable to adequately address these and other risks we face, our business, financial condition, operating results and prospects may be adversely affected.

Risk Factors

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 $90.1 million, $89.9 million, and $54.6 million for year ended December 31, 2020, 2019 and 2018, respectively. As of December 31, 2020, we had an accumulated deficit of $376.2 million. To date, we have financed our operations through sales of our capital stock and payments from the Incyte Collaboration Agreement. We have devoted substantially all of our financial resources and efforts to research and development. We expect that it may 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 for our existing clinical product candidates, telaglenastat, INCB001158, and CB-280;
- 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, commercial, regulatory and scientific personnel;
- add operational, financial and management information systems and personnel, including personnel to support product development and commercialization;
- 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/or 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, potentially prepare for commercial launch of, and seek marketing approval for our product candidates, specifically telaglenastat, and as we become obligated to make milestone payments pursuant to our outstanding license agreement. In addition, if 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 telaglenastat and CB-280;
- the costs, timing and outcome of any regulatory review of our product candidates, telaglenastat and CB-280;
- 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, or that we anticipate may 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 total remaining potential development, regulatory and commercialization milestones set forth in the Incyte Collaboration Agreement;
- 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 may not 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 the Incyte Collaboration Agreement for the development and commercialization of small molecule arginase inhibitors in hematology and oncology indications, including INCB001158, which agreement is terminable by Incyte for convenience or following our uncured breach. If the Incyte Collaboration Agreement is terminated, we would need to obtain substantial additional sources of funding to develop INCB001158 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 INCB001158 development program or dedicate resources allocated to other programs to fund INCB001158. We may also need to grant rights in the United States, as well as outside the United States, to INCB001158 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 and 2 clinical trials of our product candidates. CB-280, INCB001158, and telaglenastat are currently being evaluated in Phase 1, Phase 1/2, and Phase 2 clinical trials, respectively. 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, we may encounter unforeseen expenses, difficulties, complications, delays and other known and unknown factors that may alter or delay our plans. If a product candidate is approved, we will need to transition from a company with a research and development focus to a company capable of supporting successful commercial activities. We may not be successful in any step in such a transition.

Our ability to use our net operating loss carryforwards and certain other tax attributes may be limited.

Sections 382 and 383 place a limitation on the amount of taxable income which can be offset by carryforward tax attributes, such as net operating losses or tax credits, after a change in control. Generally, after a change in control, a loss corporation cannot deduct carryforward tax attributes in excess of the limitation prescribed by Section 382 and 383. Therefore, certain of the Company's carryforward tax attributes may be subject to an annual limitation regarding their utilization against taxable income in future periods. As a result of the Company's IPO in 2014, the Company triggered an "ownership change" as defined in Internal Revenue Code Section 382 and related provisions. Additionally, due to stock acquired by investors and reported under Section 13(g), the Company believes that an “ownership change” occurred during 2018, as well. Subsequent ownership changes since 2018 may subject the Company to annual limitations of its net operating loss and credit carryforwards. Such annual limitation could result in the expiration of the net operating loss and credit carryforwards before utilization.

Furthermore, our ability to use our net operating losses and other tax attributes to offset potential future taxable income and related income taxes that would otherwise be due is dependent upon our generation of future taxable income before the expiration dates of the net operating losses, and we cannot predict with certainty when, or whether, we will generate sufficient taxable income to use all of our net operating losses. Federal net operating losses generated prior to 2018 will continue to be governed by the net operating loss tax rules as they existed prior to the adoption of the Tax Cuts and Jobs Act of 2017, or Tax Act, which means that generally they will expire 20 years after they were generated if not used prior thereto. Under the Tax Act, as modified by the Coronavirus Aid, Relief, and Economic Security Act, or CARES Act, signed into law on March 27, 2020, federal net operating losses incurred in 2018 and in future years may be carried forward indefinitely, but the deductibility of such federal net operating losses will be limited to 80% of current year taxable income for taxable years beginning after December 31, 2020.

Our effective tax rate may fluctuate, and tax authorities may disagree with our positions and conclusions regarding certain tax positions, resulting in unanticipated costs, taxes or non-realization of expected benefits.

Our effective tax rate may be different than experienced in the past due to numerous factors, including passage of the newly enacted federal income tax law, changes in the mix of our profitability between jurisdictions in which we are or may become subject to tax, the results of examinations and audits of our tax filings, our inability to secure or sustain acceptable agreements with tax authorities, changes in accounting for income taxes and changes in tax laws. Any of these factors could cause us to experience an effective tax rate significantly different from previous periods or our current expectations and may result in tax obligations in excess of amounts accrued in our financial statements.

A tax authority may disagree with tax positions that we have taken, which could result in increased tax liabilities. For example, a tax authority could assert that we are subject to tax in a jurisdiction where we believe we have not established a taxable nexus, often referred to as a "permanent establishment" under international tax treaties, and such an assertion, if successful, could increase our expected tax liability in one or more jurisdictions. A tax authority may take the position that material income tax liabilities, interest and penalties are payable by us, in which case, we expect that we might contest such assessment. Contesting such an assessment may be lengthy and costly and if we were unsuccessful in disputing the assessment, the implications could increase our anticipated effective tax rate, where applicable.

Risks Related to Drug Discovery, Development and Commercialization

Our business, operations and clinical development plans and timelines are currently adversely affected by and could be adversely affected in the future by the effects of health epidemics, including the recent COVID-19 pandemic, on the manufacturing, clinical trial and other business activities performed by us or by third parties with whom we conduct business, including our contract manufacturers, Clinical Research Organizations, or CROs, shippers and others.

Our business could be adversely affected in the future by health epidemics wherever we have clinical trial sites or other business operations. In addition, health epidemics could cause significant disruption in the operations of third-party manufacturers, CROs and other third parties upon whom we rely. For example, in December 2019, a novel strain of coronavirus, SARS-CoV-2, causing a disease referred to as COVID-19, was reported to have surfaced in Wuhan, China. Since then, COVID-19 has spread to multiple countries worldwide, including the United States. In March 2020, the World Health Organization declared the COVID-19 outbreak a pandemic, and the U.S. government imposed travel restrictions on travel between the United States, Europe and certain other countries. Further, the President of the United States declared the COVID-19 pandemic a national emergency and invoked powers under the Stafford Act, the legislation that directs federal emergency disaster response, and under the Defense Production Act, the legislation that facilitates the production of goods and services necessary for national security and for other purposes. Similarly, the State of California declared a state of emergency related to the spread of COVID-19, and the Governor of California and other health officials in California have announced aggressive orders, health directives and recommendations to reduce the spread of the disease. On March 16, 2020, the Health Officer of San Mateo County, the county in which our headquarters is located, issued a "Shelter in Place" Order requiring, among other things, the closure of all non-essential businesses. Further, the Governor of California issued an executive order directing that all non-essential businesses close their physical operations and implement work-from-home schedules, effective as of March 19, 2020. We have implemented work-from-home policies for all employees. The effects of the executive order and our work-from-home policies may continue to negatively impact productivity, disrupt our business and delay our clinical programs and timelines, the magnitude of which will depend, in part, on the length and severity of the restrictions and other limitations on our ability to conduct our business in the ordinary course. For example, the CANTATA trial was fully enrolled in October 2019, and we previously advised that we planned to report top-line efficacy and safety data from the trial in the late third quarter or fourth quarter of 2020. In light of delays associated with COVID-19, top-line data was announced in early first quarter 2021. These and similar, and perhaps more severe, disruptions in our operations could negatively impact our business, operating results and financial condition.

We depend on a worldwide supply chain to manufacture products used in our preclinical studies and clinical trials. Quarantines, shelter-in-place and similar government orders, or the expectation that such orders, shutdowns or other restrictions could occur, whether related to COVID-19 or other infectious diseases, could impact personnel at third-party manufacturing facilities in the United States and other countries, or the availability or cost of materials, which could disrupt our supply chain.

If our relationships with our suppliers or other vendors are terminated or scaled back as a result of the COVID-19 pandemic or other health epidemics, we may not be able to enter into arrangements with alternative suppliers or vendors or do so on commercially reasonable terms or in a timely manner. Switching or adding additional suppliers or vendors involves substantial cost and requires management time and focus. In addition, there is a natural transition period when a new supplier or vendor commences work. As a result, delays may occur, which could adversely impact our ability to meet our desired clinical development and any future commercialization timelines. Although we carefully manage our relationships with our suppliers and vendors, there can be no assurance that we will not encounter challenges or delays in the future or that these delays or challenges will not harm our business.

In addition, our preclinical studies and clinical trials have been and may continue to be affected by the COVID-19 pandemic. Clinical site initiation, patient enrollment and activities that require visits to clinical sites, including data monitoring, have been and may continue to be delayed due to prioritization of hospital resources toward the COVID-19 pandemic or concerns among patients about participating in clinical trials during a pandemic. Some patients may have difficulty following certain aspects of clinical trial protocols if quarantines impede patient movement or interrupt healthcare services. Similarly, if we are unable to successfully recruit and retain patients and principal investigators and site staff who, as healthcare providers, may have heightened exposure to COVID-19 or experience additional restrictions by their institutions, city, or state our clinical trial operations could be adversely impacted.

The spread of COVID-19, which has caused a broad impact globally, may materially affect us economically. While the potential economic impact brought by, and the duration of, COVID-19 may be difficult to assess or predict, a widespread pandemic could result in significant disruption of global financial markets, reducing our ability to access capital, which could in the future negatively affect our liquidity. In addition, a recession or market correction resulting from the spread of COVID-19 could materially affect our business and the value of our common stock.

The global pandemic of COVID-19 continues to evolve rapidly. The ultimate impact of the COVID-19 pandemic or a similar health epidemic is highly uncertain and subject to change. We do not yet know the full extent of potential delays or impacts on our business, our clinical trials, healthcare systems or the global economy as a whole. However, these effects could have a material impact on our operations, and we continue to monitor the COVID-19 situation closely.

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 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 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 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.

Our drug discovery and development efforts might not generate successful product candidates.

We have invested a significant portion of our efforts and financial resources in the identification of our most advanced product candidates, telaglenastat, INCB001158 and CB-280, which are being evaluated in Phase 2, Phase 1/2 and Phase 1 clinical trials, respectively. We have entered into the Incyte Collaboration Agreement for the development and commercialization of INCB001158. Pursuant to the agreement, we and Incyte have collaborated on, and co-funded the development of, the licensed products for hematology and oncology indications, including INCB001158, with Incyte bearing 70% and Calithera bearing 30% of global development costs. Effective September 30, 2020, we have opted out of our co-development obligations and as a result, Incyte will pay all costs to develop INCB001158 or any other licensed products. All of our other programs are in research and preclinical development. Telaglenastat and INCB001158 will be developed for use in combination with other approved therapies, and as such, we will be dependent upon the continued marketing availability of the drugs that are used in combination with them. 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 may not occur for many years, if ever, will depend heavily on the successful development and eventual commercialization of telaglenastat and INCB001158. The success of telaglenastat, INCB001158 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;
- developing a sales and marketing organization or outsourcing these functions to third parties;
- launching commercial sales of the product candidates, if and when approved, whether alone or selectively in collaboration with others;
- developing and commercializing telaglenastat and small molecule arginase inhibitors, including INCB001158;
- acceptance of the product candidates, if and when approved, by patients, the medical community and third-party payors;
- effectively competing with other therapies;
- a continued acceptable safety profile of the products following approval;
- enforcing and defending intellectual property rights and claims; and

- other legal, regulatory, compliance, privacy, and fraud and abuse matters.

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 for clinical development.

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 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. For example, our CANTATA trial of telaglenastat in RCC did not meet the primary endpoint of PFS despite earlier encouraging results in this indication in a Phase 1b 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;
- 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;
- 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 the 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 health care professionals;
- 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-280, INCB001158, and telaglenastat in Phase 1, Phase 1/2, and Phase 2 clinical trials, respectively. 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 telaglenastat and INCB001158 and we have seen several adverse events, or AEs, deemed possibly or probably related to study drug in each of those programs. For example, in our evaluation of telaglenastat with nivolumab, during the dose escalation of the combination therapy, there was one report of dose limiting Grade 3 ALT increase. We have treated an insufficient number of patients to fully assess the safety of telaglenastat and INCB001158 and, as these trials progress, we may experience frequent or severe adverse events. Our ongoing and planned trials for telaglenastat and our and Incyte's ongoing and planned trials for INCB001158 may fail due to safety issues, and we may need to abandon development of telaglenastat or INCB001158. 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 INCB001158 in hematology and oncology indications. If Incyte does not successfully commercialize INCB001158, 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;
- 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 health care professionals, 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 health care professionals, 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 health care professionals to prescribe these therapies;
- the strength of marketing and distribution support;
- third-party coverage and sufficient reimbursement; and
- the prevalence and severity of any side effects.

If, in the future, we are unable to establish adequate 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 and marketing infrastructure to support any future commercialization efforts. To achieve commercial success for any approved product for which we retain sales and marketing responsibilities, we must either develop a robust sales and marketing organization and/or outsource these functions to other third parties. For our small molecule arginase inhibitors in hematology and oncology indications, including INCB001158, we will be 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, excluding INCB001158.

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 health care professionals or persuade adequate numbers of health care professionals 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 health care professionals, 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 in the fields of tumor immunology, tumor metabolism, and/or other product candidates in development for advanced cancer treatment include Agios Pharmaceuticals, Inc., Arcus Biosciences, Inc., AstraZeneca plc, Boehringer Ingelheim GmbH, Bayer Pharma AG, Bristol-Myers Squibb Company, Celgene Corporation, Corvus Pharmaceuticals, Inc., Dracen Pharmaceuticals, Inc., Eisai Co., Ltd., Eli Lilly and Company, GlaxoSmithKline plc, Incyte Corporation, iTeos Therapeutics SA, Merck & Co., Merck KGaA, Nektar Therapeutics, Novartis International AG, Pfizer Inc, Roche Holdings AG and its subsidiary Genentech, Inc., and Takeda Pharmaceutical Co., Ltd.

Our primary competitors in the field of Cystic Fibrosis include AbbVie, Inc., Beyond Air Inc., Corbus Pharmaceuticals Holdings, Inc., Novartis AG, Novoteris, LLC, Proteostatis Therapeutics, Inc., Translate Bio, Inc., and Vertex Pharmaceuticals, 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 coverage and 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 coverage and adequate 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. Coverage may not be available for any product that we commercialize and, if coverage 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 coverage 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. Coverage and 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.

In addition, there has been heightened governmental scrutiny of pharmaceutical pricing practices in light of the rising cost of prescription drugs and biologics. Such scrutiny has resulted in several recent congressional inquiries and proposed and enacted federal and state legislation designed to, among other things, bring more transparency to product pricing, review the relationship between pricing and manufacturer patient programs, and reform government program reimbursement methodologies for drug products. We expect additional healthcare reform initiatives to be adopted in the future, particularly in light of the new presidential administration. We continue to monitor and evaluate the potential impact of these legislative actions and their effect on our business and operations.

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;
- 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 manufacture our product candidates, 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, and that all clinical trial activities conducted by our contract research organizations follow applicable laws and regulations, and are conducted in an ethical and compliant manner. 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

by us, or any of the third parties working on our behalf, to do the above 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 telaglenastat, INCB001158 and CB-280 for our current and planned clinical trials from third-party manufacturers. We have engaged third party manufacturers to obtain the active ingredient for telaglenastat, INCB001158 and CB-280 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 legal and 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 legal and 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 INCB001158, is reliant in part on Incyte for the successful development and commercialization in a timely manner. If Incyte does not devote sufficient resources to INCB001158'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.

In January 2017, we and Incyte Corporation entered into the Incyte Collaboration Agreement. Pursuant to the Incyte Collaboration Agreement, we granted Incyte an exclusive, worldwide license to develop and commercialize small molecule arginase inhibitors, including INCB001158, for hematology and oncology indications. We retained rights to certain arginase inhibitors that are not part of the collaboration for specific orphan indications outside of hematology and oncology, including cystic fibrosis. Pursuant to the Incyte Collaboration Agreement, we and Incyte have collaborated on, and co-funded the development of, the licensed products for hematology and oncology indications, including INCB001158, with Incyte bearing 70% and Calithera bearing 30% of global development costs.

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 INCB001158, 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 partnership will depend on, among other things, the efforts, allocation of resources and successful development and commercialization of INCB001158;
- Incyte may select a dose for INCB001158 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; and
- Incyte may develop or commercialize INCB001158 in a way that exposes us to potential litigation that could jeopardize or invalidate our intellectual property rights or expose us to potential liability.

In April 2020, we filed a complaint against Incyte in Superior Court of California, San Francisco County, asserting claims for breach of contract arising out of Incyte's failure to pay two milestone payments we believe are due under the Incyte Collaboration Agreement. Effective September 30, 2020, we have opted out of our co-development obligations and as a result, Incyte will pay all costs to develop INCB001158 or any other licensed products. 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 INCB001158 and the development and commercialization of INCB001158 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 INCB001158, retained by us 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, for example our pending claims against Incyte, 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; and
- 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 a portfolio of arginase inhibitors as part of our efforts to develop product candidates for the arginase program, and we are substantially dependent on this in-license for that program. To the extent this in-license is terminated, our business may be harmed.

Our internal computer systems, or those used by our Clinical Research Organizations or other contractors or consultants, may fail or suffer security breaches.

Despite the implementation of security measures, our internal computer systems, and those of our Clinical Research Organizations and other third parties on which we rely, are vulnerable to damage from computer viruses and unauthorized access, malware, natural disasters, fire, terrorism, war and telecommunication, electrical failures, cyber-attacks or cyber-intrusions over the Internet, attachments to emails, persons inside our organization, or persons with access to systems inside our organization. The risk of a security breach or disruption, particularly through cyber-attacks or cyber intrusion, including by computer hackers, foreign governments, and cyber terrorists, has generally increased as the number, intensity and sophistication of attempted attacks and intrusions from around the world have increased. While we have not experienced any such material system failure or security breach to our knowledge to date, if such an event were to occur and cause interruptions in our operations, it could result in a material disruption of our development programs and our business operations. For example, the loss of clinical trial data from completed, ongoing or future clinical trials could result in delays in our regulatory approval efforts and significantly increase our costs to recover or reproduce the data. Likewise, we rely on third parties for the manufacture of our product candidates and to conduct clinical trials, and similar events relating to their computer systems could also have a material adverse effect on our business. To the extent that any disruption or security breach were to result in a loss of, or damage to, our data or applications, or inappropriate disclosure of confidential or proprietary information, we could incur liability and the further development and commercialization of our future product candidates could be delayed.

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, or fully exploit, 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.

Even if we do secure patents in foreign jurisdictions, the legal systems in certain of those countries might require us, as examples, to do business through an entity that is partially owned by a local investor, or to grant license rights to local partners in a manner not required by the jurisdictions in which we currently operate. Requirements such as the foregoing could limit our ability to fully exploit and in the future monetize our product candidates and patents, as well as placing potential additional difficulties on our enforcement efforts in those jurisdictions.

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 health care professionals 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. Physicians, on the other hand, may prescribe products for off-label uses. Although the FDA and other regulatory agencies do not regulate a physician's choice of drug treatment made in the physician's independent medical judgment, they do restrict promotional communications from companies or their sales force with respect to off-label uses of products for which marketing clearance has not been issued. Companies may only share truthful and not misleading information that is otherwise consistent with a product's FDA approved labeling.

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;
- 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 healthcare providers, 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, customers and third-party payors play a primary role in the recommendation and prescription of any product candidates for which we obtain marketing approval. Our current and 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 research, as well as 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 laws, including the False Claims Act, which can be enforced through civil whistleblower or qui tam actions, impose criminal and civil penalties 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, among other things, executing a scheme to defraud any healthcare benefit program and also imposes obligations, including mandatory contractual terms, on certain covered healthcare providers, health plans, and healthcare clearinghouses and their respective business associates that perform services for them that involve the use, or disclosure of, individually identifiable health information as well as their covered subcontractors 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 certain manufacturers of drugs, devices, biologics and medical supplies to report to the Centers for Medicare & Medicaid Services, or CMS, an agency within the Department of Health and Human Services, or HHS, information related to payments and other transfers of value to physicians (defined to include doctors, dentists, optometrists, podiatrists and chiropractors) and teaching hospitals, as well ownership and investment interests held by physicians and their immediate family members. Beginning in 2022, applicable manufacturers also will be required to report information regarding payments and other transfers of value provided to physician assistants, nurse practitioners, clinical nurse specialists, certified registered nurse anesthetists, anesthesiologist assistants, and certified nurse midwives during the previous year; 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. 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, marketing expenditures and/or drug pricing, and other state and local laws require the registration of pharmaceutical sales representatives.

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, possible exclusion from government funded healthcare programs, such as Medicare and Medicaid, disgorgement, imprisonment, integrity oversight and reporting obligations to resolve allegations of non-compliance with these laws, and the curtailment or restructuring of our operations. If any of the health care professionals 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 significant criminal, civil or administrative sanctions, including exclusions from government funded healthcare programs.

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.

Additionally, the Patient Protection and Affordable Care Act, as amended by the Health Care and Education Reconciliation Act of 2010, or collectively the PPACA, enacted in 2010, made a number of substantial changes in the way healthcare is financed by both governmental and private insurers. There continue to be significant developments in, and continued legislative activity around, attempts to repeal or repeal and replace the PPACA. Due to these efforts, there is significant uncertainty regarding the future of the PPACA.

There have been executive, judicial, and Congressional challenges to certain aspects of the PPACA. For example, the 2020 federal spending package permanently eliminated, effective January 1, 2020, the PPACA-mandated "Cadillac" tax on high-cost employer-sponsored health coverage and medical device tax and, effective January 1, 2021, also eliminated the health insurer tax. While Congress has not passed comprehensive repeal legislation, several bills affecting the implementation of certain taxes under PPACA have been signed into law. The Tax Act included a provision which repealed, effective January 1, 2019, the tax-based shared responsibility payment imposed by PPACA on certain individuals who fail to maintain qualifying health coverage for all or part of a year that is commonly referred to as the "individual mandate". On December 14, 2018, a Texas U.S. District Court Judge ruled that

the PPACA is unconstitutional in its entirety because the "individual mandate" was repealed by Congress as part of the Tax Act. Additionally, on December 18, 2019, the U.S. Court of Appeals for the 5th Circuit upheld the District Court ruling that the individual mandate was unconstitutional and remanded the case back to the District Court to determine whether the remaining provisions of the PPACA are invalid as well. The U.S. Supreme Court is currently reviewing the case, although it is unknown when a decision will be made. Further, although the U.S. Supreme Court has not yet ruled on the constitutionality of the PPACA, on January 28, 2021, President Biden issued an executive order to initiate a special enrollment period from February 15, 2021 through May 15, 2021 for purposes of obtaining health insurance coverage through the PPACA marketplace. The executive order also instructs certain governmental agencies to review and reconsider their existing policies and rules that limit access to healthcare, including among others, reexamining Medicaid demonstration projects and waiver programs that include work requirements, and policies that create unnecessary barriers to obtaining access to health insurance coverage through Medicaid or the PPACA. It is unclear how the Supreme Court ruling, other such litigation, and the healthcare reform measures of the Biden administration will impact the PPACA. We continue to evaluate the potential impact of PPACA and its possible repeal or replacement on our business.

Policy changes, including potential modification or repeal of all or parts of the PPACA or the implementation of new health care legislation could result in significant changes to the health care system, which may prevent us from being able to generate revenue, attain profitability or commercialize our drugs. We expect that additional state and federal healthcare reform measures will be adopted in the future, any of which could limit the amounts that federal and state governments will pay for healthcare products and services, which could result in reduced demand or lower pricing for our product candidates, or additional pricing pressures.

Further, there has been heightened governmental scrutiny of pharmaceutical pricing practices in light of the rising cost of prescription drugs and biologics. Such scrutiny has resulted in several recent congressional inquiries and proposed and enacted federal and state legislation designed to, among other things, bring more transparency to product pricing, review the relationship between pricing and manufacturer patient programs, and reform government program reimbursement methodologies for drug products. At the federal level, the Trump administration used several means to propose or implement drug pricing reform, including through federal budget proposals, executive orders and policy initiatives. For example, on July 24, 2020 and September 13, 2020, the Trump administration announced several executive orders related to prescription drug pricing that seek to implement several of the administration's proposals. As a result, the FDA released a final rule on September 24, 2020, effective November 30, 2020, providing guidance for states to build and submit importation plans for drugs from Canada. Further, on November 20, 2020, HHS finalized a regulation removing safe harbor protection for price reductions from pharmaceutical manufacturers to plan sponsors under Medicare Part D, either directly or through pharmacy benefit managers, unless the price reduction is required by law. The implementation of the rule has been delayed by the Biden administration from January 1, 2022 to January 1, 2023 in response to ongoing litigation. The rule also creates a new safe harbor for price reductions reflected at the point-of-sale, as well as a new safe harbor for certain fixed fee arrangements between pharmacy benefit managers and manufacturers, the implementation of which have also been delayed pending review by the Biden administration until March 22, 2021. On November 20, 2020, CMS issued an interim final rule implementing the Trump administration's Most Favored Nation executive order, which would tie Medicare Part B payments for certain physician-administered drugs to the lowest price paid in other economically advanced countries, effective January 1, 2021. On December 28, 2020, the U.S. District Court in Northern California issued a nationwide preliminary injunction against implementation of the interim final rule. It is unclear whether the Biden administration will work to reverse these measures or pursue similar policy initiatives. In addition, there have been and continue to be similar initiatives at the state level to reduce drug costs.

In addition, other legislative changes have been proposed and adopted since the PPACA was enacted. On August 2, 2011, the Budget Control Act of 2011 was signed into law, which includes reductions to Medicare payments to providers of 2% per fiscal year, which went into effect on April 1, 2013 and, due to subsequent legislative amendments to the statute will remain in effect through 2030 with the exception of a temporary suspension from May 1, 2020 through March 31, 2021 due to the COVID-19 pandemic, unless additional Congressional action is taken. It is possible that additional governmental action will be taken in response to the COVID-19 pandemic. We expect that healthcare reform measures may be adopted in the future, particularly in light of the new presidential administration, which 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 may need to expand our operations, and may encounter difficulties in managing our growth, which could disrupt our business.

In the future, we may need to expand the scope of our operations, particularly in the areas of drug development, regulatory affairs and sales and marketing. To manage our future growth, we may need 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 an expansion of our operations or recruit and train additional qualified personnel. Moreover, an 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.

International expansion of our business exposes us to business, regulatory, political, operational, financial and economic risks associated with doing business in various jurisdictions globally.

Our business strategy incorporates international expansion, including establishing and maintaining relationships with service providers, distributors and manufacturers globally. Doing business internationally involves a number of risks, including:

- multiple, conflicting and changing laws and regulations such as tax laws, export and import restrictions, employment laws, anti-bribery and anti-corruption laws, regulatory requirements and other governmental approvals, permits and licenses;
- failure by us or our distributors to obtain appropriate licenses or regulatory approvals for the sale or use of our product candidates, if approved, in various countries;
- difficulties in managing foreign operations;
- complexities of foreign reimbursement regimes and price controls;
- financial risks, such as difficulty enforcing contracts exposure to foreign currency exchange rate fluctuations;
- reduced protection for intellectual property rights;
- reduced protection of contractual rights in the event of bankruptcy or insolvency of the other contracting party;

- natural disasters, political and economic instability, including wars, terrorism and political unrest, outbreak of disease, boycotts, curtailment of trade and other business restrictions;
- difficulties in complying with changes in laws, regulations and costs affecting our foreign operations, including our United Kingdom, or UK, operations potentially affected by the UK exiting the European Union, or EU;
- failure to comply with foreign laws, regulations, standards and regulatory guidance governing the collection, use, disclosure, retention, security and transfer of personal data, including the European Union General Data Privacy Regulation, or GDPR, which introduces strict requirements for processing personal data of individuals within the European Union; and
- failure to comply with the United Kingdom Bribery Act 2010, or UK Bribery Act, and similar antibribery and anticorruption laws in other jurisdictions, and the Foreign Corrupt Practices Act, including its books and records provisions and its anti-bribery provisions, including by failing to maintain accurate information and control over sales and distributors' activities.

The UK's withdrawal from the EU, commonly referred to as Brexit, may have a negative effect on global economic conditions, financial markets and our business.

Following the result of a referendum in 2016, the United Kingdom left the European Union on January 31, 2020, commonly referred to as Brexit. Pursuant to the formal withdrawal arrangements agreed between the United Kingdom and the European Union, the United Kingdom will be subject to the Transition Period until December 31, 2020 during which European Union rules will continue to apply. Negotiations between the United Kingdom and the European Union are expected to continue in relation to the customs and trading relationship between the United Kingdom and the European Union following the expiry of the Transition Period.

The lack of clarity over which EU laws and regulations will continue to be implemented in the United Kingdom after the Transition Period (including financial laws and regulations, tax and free trade agreements, intellectual property rights, data protection laws, supply chain logistics, environmental, health and safety laws and regulations, immigration laws and employment laws) may negatively impact foreign direct investment in the United Kingdom, increase costs, depress economic activity and restrict access to capital. The uncertainty concerning the United Kingdom's legal, political and economic relationship with the European Union after the Transition Period may be a source of instability in the international markets, create significant currency fluctuations, and/or otherwise adversely affect trading agreements or similar cross-border co-operation arrangements (whether economic, tax, fiscal, legal, regulatory or otherwise).

These developments, or the perception that any of them could occur, have had, and may continue to have, a significant adverse effect on global economic conditions and the stability of global financial markets, and could significantly reduce global market liquidity and limit the ability of key market participants to operate in certain financial markets. In particular, it could also lead to a period of considerable uncertainty in relation to the United Kingdom's financial and banking markets, as well as on the regulatory process in Europe. Asset valuations, currency exchange rates and credit ratings may also be subject to increased market volatility.

If the United Kingdom and the European Union are unable to negotiate acceptable withdrawal terms or if other EU Member States pursue withdrawal, barrier-free access between the United Kingdom and other EU Member States or among the European Economic Area, or EEA, overall could be diminished or eliminated. The long-term effects of Brexit will depend on any agreements (or lack thereof) between the United Kingdom and the European Union and, in particular, any arrangements for the United Kingdom to retain access to EU markets after the Transition Period.

Such a withdrawal from the European Union is unprecedented, and it is unclear how the United Kingdom's access to the European single market for goods, capital, services and labor within the European Union, or single market, and the wider commercial, legal and regulatory environment, will impact us.

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;
- uncertainties regarding the magnitude and duration of impacts we are experiencing due to COVID-19;
- 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.

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 have and 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 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.

If we are unable to maintain proper and effective internal controls over financial reporting, the accuracy and timeliness of our financial reporting and the market price of our common stock 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. In the future, our independent registered public accounting firm may also need to attest to the effectiveness of our internal control over financial reporting.

If material weaknesses or control deficiencies occur in the future, we are unable to comply with the requirements of Section 404 in a timely manner, we are unable to assert that our internal control over financial reporting is effective, or if our independent registered public accounting firm is unable to express an opinion as to the effectiveness of our internal control over financial reporting, 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 designates the Court of Chancery of the State of Delaware and our amended and restated bylaws designate the federal district courts of the United States of America as the exclusive forums for substantially all disputes between us and our stockholders, which will restrict our stockholders' ability to choose the 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 provisions would not apply to suits brought to enforce a duty or liability created by the Exchange Act or any other claim for which the U.S. federal courts have exclusive jurisdiction. Furthermore, Section 22 of the Securities Act creates concurrent jurisdiction for federal and state courts over all such Securities Act actions. Accordingly, both state and federal courts have jurisdiction to entertain such claims. Our stockholders cannot waive compliance with the federal securities laws and the rules and regulations thereunder. To prevent having to litigate claims in multiple jurisdictions and the threat of inconsistent or contrary rulings by different courts, among other considerations, our amended and restated bylaws provide that, unless we consent in writing to the selection of an alternative forum, the federal district courts of the United States of America will be the exclusive forum for resolving any complaint asserting a cause of action arising under the Securities Act. While the Delaware courts have determined that such choice of forum provisions are facially valid, a stockholder may nevertheless seek to bring a claim in a venue other than those designated in the exclusive forum provisions. In such instance, we would expect to vigorously assert the validity and enforceability of the exclusive forum provisions of our amended and restated certificate of incorporation. This may require significant additional costs associated with resolving such action in other jurisdictions and there can be no assurance that the provisions will be enforced by a court in those other jurisdictions.

These exclusive choice of forum provisions 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 lawsuits against us and our directors, officers, and other employees. If a court were to find such exclusive-forum provisions to be inapplicable or unenforceable in an action, we may incur further significant additional costs associated with resolving the dispute in other jurisdictions, all of which could harm our business.

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. In March 2021, we entered into an amendment to our lease where we reduced our leased space to approximately 34,000 square feet. We believe that our existing facilities are adequate for our current needs.

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.

Market Information

Our common stock commenced trading on the Nasdaq Global Select Market under the symbol "CALA" on October 2, 2014.

Holders of Record

As of March 10, 2021, there were approximately 21 holders of record of our common stock.

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.

Recent Sales of Unregistered Securities

None.

Issuer Purchases of Equity Securities

None.

Item 6. Selected Financial Data.

Not required.

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

You should read the following discussion and analysis of our financial condition and results of operations in conjunction with our consolidated financial statements and related notes included in Part II, Item 8 of this report.

This discussion and analysis generally covers our financial condition and results of operations for the year ended December 31, 2020, including year-over-year comparisons versus the year ended December 31, 2019. Our Annual Report on Form 10-K for the year ended December 31, 2019, filed with the SEC on March 11, 2020, and available free of charge on the SEC's website at www.sec.gov and at our investor relations website www.calithera.com, includes a discussion and analysis of our financial condition and results of operations for the year ended December 31, 2018 in Item 7 of Part II, "Management's Discussion and Analysis of Financial Condition and Results of Operations."

This Annual Report on Form 10-K contains forward-looking statements within the meaning of Section 27A of the Securities Exchange 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. Forward-looking statements are identified by words such as "believe," "will," "may," "estimate," "continue," "anticipate," "intend," "should," "plan," "expect," "predict," "could," "potentially" or the negative of these terms or similar expressions. You should read these statements carefully because they discuss future expectations, contain projections of future results of operations or financial condition, or state other "forward-looking" information. These statements relate to our future plans, objectives, expectations, intentions and financial performance and the assumptions that underlie these statements. These forward-looking statements are subject to certain risks and uncertainties that could cause actual results to differ materially from those anticipated in the forward-looking statements. Factors that might cause such a difference include, but are not limited to, those discussed in this report in Part I, Item 1A — "Risk Factors," and elsewhere in this report. Forward-looking statements are based on our management's beliefs and assumptions and on information currently available to our management. These statements, like all statements in this report, speak only as of their date, and we undertake no obligation to update or revise these statements in light of future developments. We caution investors that our business and financial performance are subject to substantial risks and uncertainties. In addition, statements that "we believe" and similar statements reflect our beliefs and opinions on the relevant subject. These statements are based on information available to us as of the date of this Annual Report on Form 10-K. While we believe that information provides a reasonable basis for these statements, that information may be limited or incomplete. Our statements should not be read to indicate that we have conducted an exhaustive inquiry into or review of, all relevant information. These statements are inherently uncertain and investors are cautioned not to unduly rely on these statements.

Overview

We are a clinical-stage bio-pharmaceutical company focused on fighting cancer and other life-threatening diseases by discovering and developing novel small molecule drugs that target cellular metabolism. 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 created fundamentally new potential therapies for cancer patients. With our unique approach, we have established a broad pipeline of small molecule drug candidates that target enzymes controlling metabolically critical pathways in tumor cells and immune cells. We have multiple internally discovered clinical stage compounds that are all enzyme inhibitors. While we are primarily focused on oncology, we are opportunistically developing therapeutics outside of oncology where we can leverage our existing expertise in immune cell metabolism to treat diseases with unmet need.

Through genetic mutations that alter fundamental metabolic pathways, cancer cells can acquire the ability to grow in an uncontrolled manner, but they also acquire nutrient dependencies that can differentiate them from normal cells. Targeting these nutrient dependencies by inhibiting specific metabolic pathways in cancer cells is a novel therapeutic approach to blocking the uncontrolled growth of tumors. Our lead product candidate, telaglenastat or CB-839, takes advantage of the critical dependency many cancers have on the nutrient glutamine for growth and survival. We believe telaglenastat 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 first selective allosteric glutaminase inhibitor to enter clinical trials. We retain all commercial rights to telaglenastat and have been granted a U.S. patent, which includes composition of matter coverage for telaglenastat through 2037 in the U.S. and 2032 outside of the U.S.

We are currently developing telaglenastat in combination with standard therapies in a select set of solid tumors. Our lead development pathway for telaglenastat is for the treatment of KEAP1 or NRF2 mutated non-small cell lung cancer, or NSCLC. According to third-party market research, U.S. incidence of NSCLC is 192,208 with 20% of these patients harboring KEAP1 or NRF2 activating mutations. Recently presented clinical data evaluating front-line standard-of-care chemoimmunotherapy treatment for NSCLC patients with mutations in KEAP1/NRF2 demonstrated inferior clinical outcomes compared to patient without these mutations. Thus, NSCLC patients with KEAP1 or NRF2 mutations are a population with a large unmet clinical need. Pre-clinical studies have shown that activation of the KEAP1/NRF2 pathway in lung tumors makes them dependent on glutaminase activity for growth and survival, and treatment with teleglenastat selectively blocks their growth. In September 2020, we treated the first patient in the KEAPSAKE study, which is a randomized Phase 2 clinical trial of the glutaminase inhibitor telaglenastat in combination with standard-of-care therapy. The KEAPSAKE study will evaluate the safety and anti-tumor activity of telaglenastat plus standard-of-care

chemoimmunotherapy as front-line treatment for patients with stage IV non-squamous non-small cell lung cancer whose tumors have a KEAP1 or NRF2 mutation determined by next-generation sequencing. The double-blind telaglenastat trial will enroll approximately 120 patients with stage IV non-squamous NSCLC with the KEAP1 or NRF2 mutation. Patients will be randomized to receive telaglenastat or placebo, in combination with pembrolizumab, carboplatin and pemetrexed. The study will evaluate the safety and investigator assessed progression-free survival, or PFS, of telaglenastat plus this standard of care chemoimmunotherapy regimen. We anticipate sharing interim data from the KEAPSAKE trial in the second half of 2021.

We were previously developing telaglenastat for the treatment of renal cell carcinoma, or RCC. In January 2021, we announced the results of the CANTATA trial, a 444 patient global, randomized, double-blind trial designed to evaluate the safety and efficacy of telaglenastat in combination with cabozantinib versus placebo with cabozantinib in patients with advanced clear cell RCC who have been treated with one or two prior lines of systemic therapy. The trial did not meet the primary endpoint of progression-free survival, or PFS. Based on this result, we evaluated our operational and workforce needs to extend our cash runway and ensure long-term sustainability. We reduced our workforce by approximately 35% to preserve cash resources. We currently have no plans to further develop telaglenastat in RCC.

As part of our Pfizer clinical collaboration, we initiated a trial with the CDK 4/6 inhibitor IBRANCE®, in combination with telaglenastat in July 2019. The Phase 1/2 trial (NCT03965845) of the combination of telaglenastat plus Ibrance is ongoing in patients with KRAS mutated colorectal cancer and KRAS mutated non-small cell lung cancer. Encouraging efficacy and safety of the combination was observed in PDAC patients treated in the dose escalation phase of the trial. In November 2020, we announced the expansion of the study to include an additional cohort of patients with pancreatic ductal adenocarcinoma whose tumors harbor mutations in both KRAS and CDKN2A. Approximately 50 percent of PDAC patients harbor mutations in both KRAS and CDKN2A.

Our product candidate, CB-280, is an oral inhibitor of arginase, an enzyme that depletes the amino acid arginine. It is being developed for the treatment of cystic fibrosis, or CF. Arginase depletes arginine, which is critical for the generation of NO, or nitric oxide. NO has critical anti-microbial effects in lung and also mediates bronchodilation. CB-280 is a novel oral arginase inhibitor which is solely owned by Calithera. We completed a Phase 1 Single Ascending Dose trial to evaluate the safety, tolerability and pharmacokinetic profile of oral CB-280 in healthy volunteers. In July 2020, we initiated a Phase 1b clinical trial in adult patients with cystic fibrosis and chronic airway infection. The randomized, double blind, placebo-controlled, dose escalation trial will evaluate multiple ascending doses of CB-280, dosed orally twice daily for 14 days, compared to placebo in up to 32 adult CF patients to determine a safe dose range for CB-280. Enrollment in this study is ongoing and we expect to share interim data in the second half of 2021.

An additional arginase inhibitor, INCB001158, was discovered by Calithera and is being developed by Incyte Corporation, or Incyte, for oncology and hematology indications, and is currently being evaluated in Phase 1/2 trials as a monotherapy and in combination with other anti-cancer agents.

We are a fully integrated biopharmaceutical company with expertise in biology and chemistry, and our ongoing research efforts are focused on discovering additional product candidates for the treatment of cancer and other life-threatening diseases. We have discovered the clinical candidate CB-708, a potent, selective, orally administered small molecule that inhibits CD73, an enzyme that converts adenosine monophosphate to generate the immunosuppressive agent adenosine.

We have also identified CB-668, an investigational first-in-class, potent, orally administered IL4I1 inhibitor as a novel immuno-oncology approach to cancer. IL4I1 is expressed by tumor cells and antigen presenting cells and metabolizes phenylalanine, tyrosine and tryptophan to produce hydrogen peroxide, an inhibitor of T-cell function, and kynurenic acid an immunosuppressive metabolite. In syngeneic mouse models CB-668 exhibited immune mediated, single agent activity and augmented activity in combination with checkpoint inhibitors. IL4I1 expression has been correlated with poor clinical outcomes and expression is elevated in multiple tumor types including ovarian and B-cell tumors.

Critical Accounting Polices and Estimates

Our management's discussion and analysis of our financial condition and results of operations is based on our consolidated financial statements, which have been prepared in accordance with United States generally accepted accounting principles, or U.S. GAAP. The preparation of these consolidated 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 consolidated 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.

Revenue Recognition

Effective January 1, 2018, we adopted Accounting Standards Codification, or ASC, *Revenue from Contracts with Customers (Topic 606)*, or ASC 606, using the modified retrospective approach. Under this approach, we recorded a cumulative adjustment to decrease accumulated deficit and deferred revenue by $8.8 million on January 1, 2018. Under ASC 606, an entity recognizes revenue when its customer obtains control of promised goods or services, in an amount that reflects the consideration that the entity expects to receive in exchange for those goods or services. To determine revenue recognition for arrangements that an entity determines are within the scope of ASC 606, the entity performs the following five steps: (i) identify the contract(s) with a customer; (ii) identify the performance obligations in the contract; (iii) determine the transaction price; (iv) allocate the transaction price to the performance obligations in the contract; and (v) recognize revenue when (or as) the entity satisfies a performance obligation. We only apply the five-step model to contracts when it is probable that we will collect the consideration we are entitled to in exchange for the goods or services we transfer to the customer. At contract inception, once the contract is determined to be within the scope of ASC 606, we assess the goods or services promised within each contract and determine those that are performance obligations, and assess whether each promised good or service is distinct. We then recognize as revenue the amount of the transaction price that is allocated to the respective performance obligation when (or as) the performance obligation is satisfied.

We have a collaboration and licensing agreement that is within the scope of ASC 606, under which we license certain rights to one of our product candidates to Incyte Corporation. The terms of this arrangement include payment to us of a non-refundable, upfront license fee, and potential development, regulatory and sales milestones, and sales royalties. Each of these payments results in collaboration revenues, except for revenues from royalties on net sales of licensed products, which would be classified as royalty revenues.

In determining the appropriate amount of revenue to be recognized as we fulfill our obligations under our agreement, we perform the following steps: (i) identification of the promised goods or services in the contract; (ii) determination of whether the promised goods or services are performance obligations including whether they are distinct in the context of the contract; (iii) measurement of the transaction price, including the constraint on variable consideration; (iv) allocation of the transaction price to the performance obligations; and (v) recognition of revenue when (or as) we satisfy each performance obligation. As part of the accounting for these arrangements, we must develop assumptions that require judgment to determine the stand-alone selling price for each performance obligation identified in the contract.

Licenses of Intellectual Property: If the license to our intellectual property is determined to be distinct from the other performance obligations identified in the arrangement, we recognize revenues from non-refundable, upfront fees allocated to the license when the license is transferred to the licensee and the licensee is able to use and benefit from the license. For licenses that are bundled with other promised goods or services, we utilize judgment to assess the nature of the combined performance obligation to determine whether the combined performance obligation is satisfied over time or at a point in time and, if over time, the appropriate method of measuring progress for purposes of recognizing revenue from non-refundable, upfront fees. We evaluate the measure of progress each reporting period and, if necessary, adjust the measure of performance and related revenue recognition.

Milestone Payments: At the inception of each arrangement that includes development, regulatory or commercial milestone payments, we evaluate whether the milestones are considered probable of being reached and estimate the amount to be included in the transaction price. If it is probable that a significant reversal of cumulative revenue would not occur, the associated milestone value is included in the transaction price. Milestone payments that are not within our control or the licensees' control, such as regulatory approvals, are not considered probable of being achieved until those approvals are received or the underlying activity has been completed. The transaction price is then allocated to each performance obligation on a relative stand-alone selling price basis, for which we recognize revenue as or when the performance obligations under the contract are satisfied. At the end of each subsequent reporting period, we re-evaluate the probability of achievement of such development milestones and any related constraint, and if necessary, adjust our estimate of the overall transaction price. Any such adjustments are recorded on a cumulative catch-up basis, which would affect collaboration revenue in the period of adjustment.

Royalties: For arrangements that include sales-based royalties, including milestone payments based on the level of sales, and the license is deemed to be the predominant item to which the royalties relate, we recognize revenue at the later of (i) when the related sales occur, or (ii) when the performance obligation to which some or all of the royalty has been allocated has been satisfied (or partially satisfied). To date, we have not recognized any royalty revenue resulting from any of our licensing arrangements.

Contract Balances

Upfront payments and fees are recorded as deferred revenue upon receipt or when due, and may require deferral of revenue recognition to a future period until we perform our obligations under these arrangements. Amounts payable to us are recorded as accounts receivable when our right to consideration is unconditional.

We receive payments from Incyte based on billing schedules established in the contract. Upfront payments and fees are recorded as deferred revenue upon receipt or when due, and may require deferral of revenue recognition to a future period until we perform our obligations under these arrangements. Amounts are recorded as accounts receivable when our right to consideration is unconditional. We do not assess whether a contract has a significant financing component if the expectation at contract inception is such that the period between payment by the licensees and the transfer of the promised goods or services to the licensees will be one year or less.

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 and clinical studies, 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 sheets and within research and development expense in the statements of operations. These costs are a significant component of our research and development expenses. We accrue for these costs based on factors such as estimates of the work completed and in accordance with agreements established with our third-party service providers under the service agreements.

We have not experienced any material differences between accrued costs and actual costs incurred. However, the status and timing of actual services performed, number of patients enrolled, and the rate of patient enrollments may vary from our estimates, resulting in adjustments to expense in future periods. Changes in these estimates that result in material changes to our accruals could materially affect our results of operations.

Financial Overview

Collaboration Revenue

Collaboration revenue represents the portion of deferred revenue recognized from a $45.0 million upfront fee and $12.0 million milestone achieved in the first quarter of 2017, from the Incyte Collaboration Agreement. The combined transaction price of $57.0 million was recognized over the estimated period of performance under the Incyte Collaboration Agreement based on the measure of progress toward completion for the combined performance obligation, which was satisfied as of June 2018. Effective January 1, 2018, we adopted ASC 606 using the modified retrospective approach. Refer to Item 8, Notes to consolidated financial statements, Notes 2 and 11, for further information on the adoption of ASC 606 and the Incyte Collaboration Agreement.

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. Costs associated with co-development activities performed under our collaboration agreements with Incyte, Bristol-Myers Squibb, and Pfizer and activity performed under our award with the Cystic Fibrosis Foundation are included in research and development expenses, with any reimbursement of costs reflected as a reduction of such expenses.

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 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 2020 and 2019:

	Year Ended December 31,	
	2020	2019
	(in thousands)	
Development candidate:		
Telaglenastat (CB-839)	$ 53,776	$ 51,019
INCB001158	4,133	10,336
CB-280	5,998	4,002
Total development	63,907	65,357
Preclinical and research:		
Preclinical and research	7,108	10,933
Total	$ 71,015	$ 76,290

We expect our research and development expenses will decrease over the next year primarily due to the completion of our CANTATA trial and our workforce reduction announced in January 2021.

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, insurance, investor relations and other expenses associated with being a public company. 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 expense and other supplies. We expect our general and administrative expenses will decrease over the next year.

Results of Operations

Comparison of the Years Ended December 31, 2020 and 2019

	Years Ended December 31,		Change	
	2020	2019	$	%
	(in thousands, except percentages)			
Operating expenses:				
Research and development	$ 71,015	$ 76,290	$ (5,275)	-7%
General and administrative	20,372	16,605	3,767	23%
Total operating expenses	91,387	92,895	(1,508)	-2%
Loss from operations	(91,387)	(92,895)	1,508	-2%
Interest and other income, net	1,250	3,035	(1,785)	-59%
Net loss	$ (90,137)	$ (89,860)	$ (277)	0%

Research and Development

Research and development expenses decreased $5.3 million, or 7%, from $76.3 million for 2019 to $71.0 million for 2020. The decrease of $5.3 million was due to a $6.2 million decrease in the INCB001158 program and a $3.8 million decrease in our early stage research programs, partially offset by an increase of $2.7 million in the telaglenastat program and an increase of $2.0 million in the CB-280 program.

General and Administrative

General and administrative expenses increased $3.8 million, or 23%, from $16.6 million for 2019 to $20.4 million for 2020. The increase of $3.8 million was primarily related to a $2.5 million increase in personnel-related and facility costs, primarily from increases in headcount, salaries, stock-based compensation expense and the expansion of our office space, and a $1.3 million increase in professional services costs, mainly for activities related to commercial preparation and the potential launch of telaglenastat and legal services related to our complaint filed against Incyte.

Interest and Other Income, net

Interest and other income, net decreased $1.8 million, from $3.0 million for the year ended December 31, 2019 to $1.2 million for the year ended December 31, 2020. The decrease of $1.8 million was primarily due to lower interest income generated from lower returns on our investments.

Liquidity and Capital Resources

As of December 31, 2020, we had cash, cash equivalents and investments totaling $115.2 million. Our operations have been financed by net proceeds from the sale of shares of our capital stock and payments from the Incyte Collaboration Agreement.

In August 2020, we filed a shelf 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 $250 million of our common stock. As of December 31, 2020, $250 million of our common stock remained available for sale, of which $75 million may be issued and sold pursuant to an at-the-market offering program for sales of our common stock under a sales agreement with Jefferies LLC, subject to certain conditions as specified in the sales agreement.

In April 2020, we sold 5,750,000 shares of our common stock pursuant to an underwriting agreement with Citigroup Global Markets, Inc. The public offering price was $6.25 per share for gross proceeds of $35.9 million, resulting in net proceeds of approximately $33.5 million after deducting underwriting fees and offering expenses.

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, 2020 will be sufficient for us to meet our current operating plan for at least the twelve-month period following the filing of our December 31, 2020 Form 10-K. 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 based on a number of factors including the extent and magnitude of the impact from the COVID-19 pandemic, in particular the challenges associated with opening new clinical studies. 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 further 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. The continued spread of COVID-19 and uncertain market conditions may limit our ability to access capital. 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,	
	2020	2019
	(in thousands)	
Cash used in operating activities	$ (84,312)	$ (78,745)
Cash provided by (used in) investing activities	$ 88,960	$ (10,784)
Cash provided by financing activities	$ 42,061	$ 98,908

Cash Flows

Year Ended 2020 Compared with Year Ended 2019

Cash used in operations was $84.3 million for 2020, compared to $78.7 million for 2019. The increase of $5.6 million in cash used in operations was primarily due to the timing of payments.

Cash provided by (used in) investing activities was $89.0 million and ($10.8) million in 2020 and 2019, respectively, and for both years primarily related to the purchase and the sale and maturity of investments.

Cash provided by financing activities was $42.1 million and $98.9 million in 2020 and 2019, respectively. For 2020, we received $33.5 million in net proceeds from the sale and issuance of common stock related to our public offering, $7.4 million in net proceeds from the issuance of common stock through our at-the-market offering program, and $1.2 million from the issuance of common stock upon the exercise of stock options and from employee stock plan purchases. In 2019, we received $53.8 million in net proceeds from the sale and issuance of common stock related to our public offering, $43.9 million in net proceeds from the issuance of common stock through our at-the-market offering programs, and $1.2 million from the issuance of common stock upon the exercise of stock options and from employee stock plan purchases.

Off-Balance Sheet Arrangements

During 2020 and 2019 we did not have any off-balance sheet arrangements.

Recent Accounting Pronouncements

Please refer to Note 2 to our audited consolidated financial statements appearing under Part II, Item 8 for a discussion of recent accounting pronouncements.

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

Not required.

Item 8. Consolidated Financial Statements and Supplementary Data.

CALITHERA BIOSCIENCES, INC.

INDEX TO CONSOLIDATED FINANCIAL STATEMENTS

Report of Independent Registered Public Accounting Firm

To the Stockholders and the Board of Directors of Calithera Biosciences, Inc.

Opinion on the Financial Statements

We have audited the accompanying consolidated balance sheets of Calithera Biosciences, Inc. (the Company) as of December 31, 2020 and 2019, the related consolidated statements of operations, comprehensive loss, stockholders' equity and cash flows for each of the three years in the period ended December 31, 2020, and the related notes (collectively referred to as the "consolidated financial statements"). In our opinion, the consolidated financial statements present fairly, in all material respects, the financial position of the Company at December 31, 2020 and 2019, and the results of its operations and its cash flows for each of the three years in the period ended December 31, 2020, in conformity with U.S. generally accepted accounting principles.

Basis for Opinion

These financial statements are the responsibility of the Company's management. Our responsibility is to express an opinion on the Company's financial statements based on our audits. We are a public accounting firm registered with the Public Company Accounting Oversight Board (United States) (PCAOB) and are required to be independent with respect to the Company in accordance with the U.S. federal securities laws and the applicable rules and regulations of the Securities and Exchange Commission and the PCAOB.

We conducted our audits in accordance with the standards of the PCAOB. Those standards require that we plan and perform the audit to obtain reasonable assurance about whether the financial statements are free of material misstatement, whether due to error or fraud. The Company is not required to have, nor were we engaged to perform, an audit of its internal control over financial reporting. As part of our audits we are required to obtain an understanding of internal control over financial reporting 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.

Our audits included performing procedures to assess the risks of material misstatement of the financial statements, whether due to error or fraud, and performing procedures that respond to those risks. Such procedures included examining, on a test basis, evidence regarding the amounts and disclosures in the financial statements. Our audits also included evaluating the accounting principles used and significant estimates made by management, as well as evaluating the overall presentation of the financial statements. We believe that our audits provide a reasonable basis for our opinion.

Critical Audit Matter

The critical audit matter communicated below is a matter arising from the current period audit of the financial statements that was communicated or required to be communicated to the audit committee and that: (1) relates to accounts or disclosures that are material to the financial statements and (2) involved our especially challenging, subjective or complex judgments. The communication of the critical audit matter does not alter in any way our opinion on the consolidated financial statements, taken as a whole, and we are not, by communicating the critical audit matter below, providing a separate opinion on the critical audit matter or on the account or disclosure to which it relates.

Accrued research and development expenses

Description of the Matter	As of December 31, 2020, the Company accrued $7.9 million of clinical and contract manufacturing expenses. As described in Note 2 to the consolidated financial statements, the Company records accrued liabilities for estimated costs of research and development activities based upon the estimated amount of services provided but not yet invoiced. The Company accrues for these costs based on factors such as estimates of the work completed under service agreements established with its third-party service providers. Auditing management's accounting for accrued research and development expenses was especially challenging because the analysis is dependent upon data exchanged between internal clinical personnel and third-party service providers. The determination of the accrual when the Company has either not been invoiced or has not received information regarding actual costs incurred requires evaluation of the status and timing of actual services performed, number of patients enrolled, and the rate of patient enrollments, which is tracked in spreadsheets and other end user computing programs.

How We Addressed the Matter in Our Audit	To test the Company's accrued clinical and contract manufacturing expenses, our audit procedures included, among others, testing the completeness and accuracy of management's calculations of activities performed for significant clinical trials. We investigated significant fluctuations or the absence of expected fluctuations in the accrual balances and agreed amounts underlying the accrual balances to supporting agreements, change orders, assessments of the level of effort incurred, estimated timelines, invoices and payment documentation. We met with clinical personnel outside of the accounting department to discuss the basis of significant accruals. Further, we tested a sample of actual invoices paid to third parties both before and after the balance sheet date to determine whether services performed had been properly recorded.

/s/ Ernst & Young LLP

We have served as the Company's auditor since 2014.
Redwood City, California
March 16, 2021

Calithera Biosciences, Inc.
Consolidated Balance Sheets
(in thousands, except per share amounts)

	December 31, 2020	December 31, 2019
Assets		
Current assets:		
Cash and cash equivalents	$ 107,146	$ 60,437
Short-term investments	8,005	96,924
Receivables from collaborations	1,541	482
Prepaid expenses and other current assets	2,011	1,953
Total current assets	118,703	159,796
Other assets	—	280
Restricted cash	440	440
Property and equipment, net	690	992
Operating lease right-of-use asset	5,754	7,260
Total assets	$ 125,587	$ 168,768
Liabilities and Stockholders' Equity		
Current liabilities:		
Accounts payable	$ 1,994	$ 2,052
Accrued and other liabilities	16,407	17,572
Total current liabilities	18,401	19,624
Noncurrent operating lease liability	4,815	6,718
Total liabilities	23,216	26,342
Commitments and contingencies (Note 5)		
Stockholders' equity:		
Preferred stock, $0.0001 par value, 10,000 shares authorized as of December 31, 2020 and 2019; no shares issued and outstanding as of December 31, 2020 and 2019	—	—
Common stock, $0.0001 par value, 200,000 shares authorized as of December 31, 2020 and 2019; 70,686 and 63,514 shares issued and outstanding as of December 31, 2020 and 2019, respectively	7	6
Additional paid-in capital	478,599	428,479
Accumulated deficit	(376,238)	(286,101)
Accumulated other comprehensive income	3	42
Total stockholders' equity	102,371	142,426
Total liabilities and stockholders' equity	$ 125,587	$ 168,768

See accompanying notes.

Calithera Biosciences, Inc.
Consolidated Statements of Operations
(in thousands, except per share amounts)

	Year Ended December 31,		
	2020	2019	2018
Revenue:			
Collaboration revenue	$ —	$ —	$ 22,254
Total revenue	—	—	22,254
Operating expenses:			
Research and development	71,015	76,290	66,195
General and administrative	20,372	16,605	13,340
Total operating expenses	91,387	92,895	79,535
Loss from operations	(91,387)	(92,895)	(57,281)
Interest and other income, net	1,250	3,035	2,652
Net loss	$ (90,137)	$ (89,860)	$ (54,629)
Net loss per share, basic and diluted	$ (1.31)	$ (1.90)	$ (1.49)
Weighted average common shares used to compute net loss per share, basic and diluted	68,814	47,312	36,604

See accompanying notes.

Calithera Biosciences, Inc.
Consolidated Statements of Comprehensive Loss
(in thousands)

	Year Ended December 31,		
	2020	2019	2018
Net loss	$ (90,137)	$ (89,860)	$ (54,629)
Other comprehensive income (loss):			
Net unrealized gain (loss) on available-for-sale securities	(39)	155	157
Total comprehensive loss	$ (90,176)	$ (89,705)	$ (54,472)

See accompanying notes.

Calithera Biosciences, Inc.
Consolidated Statements of Stockholders' Equity
(in thousands, except per share amounts)

	Common Stock		Additional Paid-In Capital	Accumulated Deficit	Accumulated Other Comprehensive Income (Loss)	Total Stockholders' Equity
	Shares	Amount				
Balance at December 31, 2017	35,759	$ 4	$300,906	$ (150,333)	$ (270)	$ 150,307
Issuance of common stock in connection with at-the-market offering, net of underwriting commissions and issuance costs	2,731	—	13,729	—	—	13,729
Exercise of stock options	125	—	247	—	—	247
Issuance of common stock per ESPP purchase	219	—	674	—	—	674
Stock-based compensation expense	—	—	7,437	—	—	7,437
Cumulative-effect adjustment from adoption of ASC 606 accounting standard on revenue recognition	—	—	—	8,792	—	8,792
Net loss	—	—	—	(54,629)	—	(54,629)
Unrealized gain on available-for-sale securities	—	—	—	—	157	157
Balance at December 31, 2018	38,834	4	322,993	(196,170)	(113)	126,714
Issuance of common stock in connection with public offering, net of underwriting commissions and issuance costs	14,375	1	53,760	—	—	53,761
Issuance of common stock in connection with at-the-market offerings, net of underwriting commissions and issuance costs	9,929	1	43,967	—	—	43,968
Exercise of stock options	191	—	490	—	—	490
Issuance of common stock per ESPP purchase	185	—	732	—	—	732
Stock-based compensation expense	—	—	6,466	—	—	6,466
Cumulative-effect adjustment from adoption of ASU 2018-07 accounting standard on stock compensation	—	—	71	(71)	—	—
Net loss	—	—	—	(89,860)	—	(89,860)
Unrealized gain on available-for-sale securities	—	—	—	—	155	155
Balance at December 31, 2019	63,514	6	428,479	(286,101)	42	142,426
Issuance of common stock in connection with public offering, net of underwriting commissions and issuance costs	5,750	1	33,463	—	—	33,464
Issuance of common stock in connection with at-the-market offering, net of underwriting commissions and issuance costs	1,160	—	7,397	—	—	7,397
Exercise of stock options	64	—	407	—	—	407
Issuance of common stock per ESPP purchase	198	—	793	—	—	793
Stock-based compensation expense	—	—	8,060	—	—	8,060
Net loss	—	—	—	(90,137)	—	(90,137)
Unrealized loss on available-for-sale securities	—	—	—	—	(39)	(39)
Balance at December 31, 2020	70,686	$ 7	$478,599	$ (376,238)	$ 3	$ 102,371

See accompanying notes.

Calithera Biosciences, Inc.
Consolidated Statements of Cash Flows
(in thousands)

	Year Ended December 31,		
	2020	2019	2018
Cash Flows Used in Operating Activities			
Net loss	$ (90,137)	$ (89,860)	$ (54,629)
Adjustments to reconcile net loss to net cash used in operating activities:			
Depreciation	364	479	505
Amortization of premiums on investments	(142)	(897)	(272)
Stock-based compensation	8,060	6,466	7,437
Non-cash lease expense	1,506	1,366	—
Changes in operating assets and liabilities:			
Receivables from collaborations	(1,059)	1,515	(855)
Prepaid expenses and other current assets	(58)	(26)	630
Other assets	280	289	(341)
Accounts payable	(58)	816	175
Accrued liabilities	(1,590)	2,576	4,725
Lease liability	(1,478)	(1,469)	—
Deferred revenue	—	—	(22,254)
Deferred rent, non-current	—	—	37
Net cash used in operating activities	(84,312)	(78,745)	(64,842)
Cash Flows Provided by (Used in) Investing Activities			
Purchases of investments	(57,059)	(153,227)	(76,107)
Proceeds from the sale and maturity of investments	146,080	142,450	129,120
Purchase of property and equipment	(61)	(7)	(214)
Net cash provided by (used in) investing activities	88,960	(10,784)	52,799
Cash Flows Provided by Financing Activities			
Proceeds from issuance of common stock upon public offering, net	33,464	53,760	—
Proceeds from issuance of common stock through at-the-market offerings, net	7,397	43,926	13,705
Proceeds from stock option exercises and employee stock plan purchases	1,200	1,222	921
Net cash provided by financing activities	42,061	98,908	14,626
Net increase in cash, cash equivalents, and restricted cash	46,709	9,379	2,583
Cash, cash equivalents, and restricted cash at beginning of period	60,877	51,498	48,915
Cash, cash equivalents, and restricted cash at end of period	$ 107,586	$ 60,877	$ 51,498

See accompanying notes.

1. Organization and Basis of Presentation

Organization

Calithera Biosciences, Inc., or the Company, was incorporated in the State of Delaware on March 9, 2010. The Company is a clinical-stage biopharmaceutical company pioneering the discovery and development of targeted therapies that disrupt cellular metabolic pathways to preferentially block tumor cells and enhance immune-cell activity. Driven by a commitment to rigorous science and a passion for improving the lives of people impacted by cancer and other life-threatening diseases, Calithera is advancing a pipeline of first-in-clinic, oral therapeutics to meaningfully expand treatment options available to patients. The Company's principal operations are based in South San Francisco, California, and it operates in one segment.

Presentation

The consolidated financial statements include the accounts of the Company and its wholly-owned subsidiaries, Calithera Biosciences UK Limited and Calithera Biosciences Ireland Limited. All significant intercompany accounts and transactions have been eliminated from the consolidated financial statements.

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 $376.2 million as of December 31, 2020. 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 2020 consolidated financial statements included in the Annual Report 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 consolidated financial statements have been prepared in accordance with U.S. generally accepted accounting principles, or GAAP. The preparation of consolidated 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 consolidated financial statements and the reported amounts of revenues and expenses during the reporting period. On an ongoing basis, management evaluates its estimates, including those related to clinical trial accrued liabilities, revenue recognition, 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 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 and other income, net. The cost of securities sold is based on the specific-identification method. Interest on marketable securities is included in interest and other income, net.

Receivables from Collaborations

Receivables from collaborations represent amounts due under the terms of the Company's collaboration agreements and awards, primarily its collaboration agreement with Incyte Corporation, or Incyte, as described in Note 11, Collaboration and Licensing Agreements - *Incyte Collaboration and License Agreement*, for reimbursements of certain costs. Based on its evaluation of credit worthiness and historical payment patterns, the Company did not record any allowance for doubtful accounts as of December 31, 2020 and 2019.

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.

All of the Company's collaboration revenue and the majority of the Company's receivables from collaborations are derived from its collaboration and license agreement with Incyte Corporation, or Incyte, as described in Note 11, Collaboration and Licensing Agreements - *Incyte Collaboration and License Agreement*.

Property and Equipment

Property and equipment are stated at cost, less accumulated depreciation. Depreciation is computed using the straight-line method over the estimated useful lives of the respective assets. Depreciation 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 is 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 equipment	5 years
Furniture and office equipment	5 years
Computer equipment	3 years
Software	3 years
Leasehold improvements	Shorter of remaining lease term or estimated useful life

Impairment of Long-Lived Assets

The Company evaluates its long-lived assets, including property and equipment, for impairment whenever events or changes in circumstances indicate that the carrying value of these assets may not be recoverable. Recoverability of these assets is measured by comparison of the carrying amount of each asset to the future undiscounted cash flows the asset is expected to generate over its remaining life. If the asset is considered to be impaired, the amount of any impairment is measured as the difference between the carrying value and the fair value of the impaired asset. The Company has not recorded impairment of any long-lived assets during any of the periods presented.

Revenue Recognition

The Company records revenue in accordance with Accounting Standards Codification, or ASC, *Revenue from Contracts with Customers (Topic 606),* or ASC 606. Under ASC 606, an entity recognizes revenue when its customer obtains control of promised goods or services, in an amount that reflects the consideration that the entity expects to receive in exchange for those goods or services. To determine revenue recognition for arrangements that an entity determines are within the scope of ASC 606, the entity performs the following five steps: (i) identify the contract(s) with a customer; (ii) identify the performance obligations in the contract; (iii) determine the transaction price; (iv) allocate the transaction price to the performance obligations in the contract; and (v) recognize revenue when (or as) the entity satisfies a performance obligation. The Company only applies the five-step model to contracts when it is probable that the entity will collect the consideration it is entitled to in exchange for the goods or services it transfers to the customer. At contract inception, once the contract is determined to be within the scope of ASC 606, the Company assesses the goods or services promised within each contract and determines those that are performance obligations, and assesses whether each promised

good or service is distinct. The Company then recognizes as revenue the amount of the transaction price that is allocated to the respective performance obligation when (or as) the performance obligation is satisfied.

The Company has a collaboration and license agreement with Incyte, or the Incyte Collaboration Agreement, that is within the scope of ASC 606, under which it licenses certain rights to one of its product candidates to Incyte Corporation. The terms of this arrangement include payment to the Company of a non-refundable, upfront license fee, and potential development, regulatory and sales milestones, and sales royalties. Each of these payments results in collaboration revenues, except for revenues from royalties on net sales of licensed products, which would be classified as royalty revenues.

In determining the appropriate amount of revenue to be recognized as it fulfills its obligations under its agreement, the Company performs the following steps: (i) identification of the promised goods or services in the contract; (ii) determination of whether the promised goods or services are performance obligations including whether they are distinct in the context of the contract; (iii) measurement of the transaction price, including the constraint on variable consideration; (iv) allocation of the transaction price to the performance obligations; and (v) recognition of revenue when (or as) the Company satisfies each performance obligation. As part of the accounting for these arrangements, the Company must develop assumptions that require judgment to determine the stand-alone selling price for each performance obligation identified in the contract.

Licenses of Intellectual Property: If the license to the Company's intellectual property is determined to be distinct from the other performance obligations identified in the arrangement, the Company recognizes revenues from non-refundable, upfront fees allocated to the license when the license is transferred to the licensee and the licensee is able to use and benefit from the license. For licenses that are bundled with other promised goods or services, the Company utilizes judgment to assess the nature of the combined performance obligation to determine whether the combined performance obligation is satisfied over time or at a point in time and, if over time, the appropriate method of measuring progress for purposes of recognizing revenue from non-refundable, upfront fees. The Company evaluates the measure of progress each reporting period and, if necessary, adjusts the measure of performance and related revenue recognition.

Milestone Payments: At the inception of each arrangement that includes development, regulatory or commercial milestone payments, the Company evaluates whether the milestones are considered probable of being reached and estimates the amount to be included in the transaction price. If it is probable that a significant reversal of cumulative revenue would not occur, the associated milestone value is included in the transaction price. Milestone payments that are not within the control of the Company or the licensee, such as regulatory approvals, are not considered probable of being achieved until those approvals are received or the underlying activity has been completed. The transaction price is then allocated to each performance obligation on a relative stand-alone selling price basis, for which the Company recognizes revenue as or when the performance obligations under the contract are satisfied. At the end of each subsequent reporting period, the Company re-evaluates the probability of achievement of such development milestones and any related constraint, and if necessary, adjusts its estimate of the overall transaction price. Any such adjustments are recorded on a cumulative catch-up basis, which would affect collaboration revenue in the period of adjustment.

Royalties: For arrangements that include sales-based royalties, including milestone payments based on the level of sales, and the license is deemed to be the predominant item to which the royalties relate, the Company recognizes revenue at the later of (i) when the related sales occur, or (ii) when the performance obligation to which some or all of the royalty that has been allocated has been satisfied (or partially satisfied). To date, the Company has not recognized any royalty revenue resulting from any of its licensing arrangements.

Contract Balances

Upfront payments and fees are recorded as deferred revenue upon receipt or when due, and may require deferral of revenue recognition to a future period until the Company performs its obligations under these arrangements. Amounts payable to the Company are recorded as accounts receivable when the Company's right to consideration is unconditional.

The Company does not assess whether a contract has a significant financing component if the expectation at contract inception is such that the period between payment by the licensees and the transfer of the promised goods or services to the licensees will be one year or less.

Deferred revenue related to the Incyte Collaboration Agreement, which was comprised of the $57 million transaction price including a $45 million upfront license payment and a $12 million development milestone achieved, less the collaboration revenue recognized from the effective date of the contract, was recognized as the combined performance obligation was satisfied.

The Company had no contract assets during the years ended December 31, 2020 and 2019. The Company had no contract liabilities during the year ended December 31, 2020 and 2019. During the year ended December 31, 2018, the Company's contract liabilities, which consisted of deferred revenue, decreased $31.0 million related to revenue recognized in the period related to amounts included in the contract liability at the beginning of the period. In addition, the Company recorded a cumulative adjustment to decrease accumulated deficit and deferred revenue by $8.8 million upon the adoption of ASC 606 on January 1, 2018, using the modified retrospective approach. For the years ended December 31, 2020, 2019 and 2018, the Company did not recognize any revenue from performance obligations satisfied in previous periods.

Accrued Research and Development Costs

The Company records accrued liabilities for estimated costs of research and development activities conducted by third-party service providers, which include the conduct of preclinical and clinical studies, and contract manufacturing activities. The Company records the estimated costs of research and development activities based upon the estimated amount of services provided but not yet invoiced, and includes these costs in accrued and other liabilities in the consolidated balance sheets and within research and development expense in the consolidated statements of operations. These costs are a significant component of the Company's research and development expenses. The Company accrues for these costs based on factors such as estimates of the work completed and in accordance with agreements established with its third-party service providers under the service agreements. The Company makes significant judgments and estimates in determining the accrued liabilities balance in each reporting period. As actual costs become known, the Company adjusts its accrued liabilities. The Company has not experienced any material differences between accrued costs and actual costs incurred. However, the status and timing of actual services performed, number of patients enrolled, and the rate of patient enrollments may vary from the Company's estimates, resulting in adjustments to expense in future periods. Changes in these estimates that result in material changes to the Company's accruals could materially affect the Company's results of operations.

Research and Development Costs

Research and development costs are expensed as incurred and consist of salaries and benefits, stock-based compensation expense, laboratory supplies, manufacturing costs, and allocated facility costs, as well as fees paid to third parties that conduct certain research and development activities on the Company's behalf. Costs associated with development activities performed under the collaboration agreements and awards are included in research and development expenses, with any reimbursement of costs reflected as a reduction of such expenses. Nonrefundable advance payments for goods or services to be rendered in the future for use in research and development activities are deferred and capitalized. The capitalized amounts are expensed as the related goods are delivered or the services are performed.

Awards

The Company assesses at the inception of award agreements whether the agreement is a liability. If the Company is obligated to repay funds received regardless of the outcome of the related research and development activities, then the Company is required to estimate and recognize a liability for this obligation. Alternatively, if the Company is not required to repay the funds, then payments received are recorded as contra research and development expense in the consolidated statement of operations as expenses are incurred.

Receivables from collaborations represent amounts receivable for which the payment criteria has been met and allowable expenses have been incurred, but not received as of the balance sheet date. Collaboration reimbursement advances represent amounts received for which the allowable expenses have not been incurred as of the balance sheet date.

Deferred Rent

Rent expense is recognized on a straight-line basis over the noncancelable term of the Company's operating lease. Prior to the adoption of ASU NO. 2016-02, *Leases (Topic 842),* or ASU 842, the Company recorded the difference between cash rent payments and the recognition of rent expense as a deferred rent liability. Incentives granted under the Company's facility leases, including allowances to fund leasehold improvements, are deferred and are recognized as adjustments to rental expense on a straight-line basis over the term of the lease.

Leases

Effective January 1, 2019, the Company adopted ASU No. 2016-02, *Leases (Topic 842),* or ASU 842. Operating lease right-of-use, or ROU, assets and lease liabilities are recognized at commencement and are recorded for leases with durations greater than 12 months.

ROU assets represent the Company's right to use an underlying asset during the lease term, and lease liabilities represent the Company's obligation to make lease payments arising from the lease. The Company's lease terms may include options to extend or terminate the lease when it is reasonably certain that it will exercise that option. Operating lease ROU assets and liabilities are recognized at commencement date based on the present value of lease payments over the lease term. The Company estimates an incremental borrowing rate based on the information available at commencement date, in determining the present value of lease payments. The operating lease ROU asset also includes lease incentives. The Company elected to not separate lease components and non-lease components for its long-term facility lease. Variable lease payments include lease operating expenses.

Stock-Based Compensation

Stock-based awards issued to employees, non-employee directors of the board, and non-employees, including stock options and stock purchased under the employee stock purchase plan, are recorded at fair value as of the grant date using the Black-Scholes option-pricing model and recognized as expense on a ratable basis over the employee or director's requisite service period (generally the vesting period).

Because stock compensation expense is based on awards ultimately expected to vest, it is reduced by forfeitures. The Company has elected to account for forfeitures as they occur.

Income Taxes

The Company uses the liability method of accounting for income taxes. Under this method, deferred tax assets and liabilities are determined based on the differences between the financial reporting and the tax bases of assets and liabilities and are measured using the enacted tax rates and laws that will be in effect when the differences are expected to reverse. The Company must then assess the likelihood that the resulting deferred tax assets will be realized. A valuation allowance is provided when it is more likely than not that some portion or all of a deferred tax asset will not be realized. Since realization of the Company's deferred tax assets is dependent upon the Company generating future taxable income, the timing and amount of which are uncertain, the net deferred tax assets have been fully offset by a valuation allowance.

The Company recognizes benefits of uncertain tax positions if it is more likely than not that such positions will be sustained upon examination based solely on their technical merits, as the largest amount of benefit that is more likely than not to be realized upon the ultimate settlement. The Company's policy is to recognize interest and penalties related to the underpayment of income taxes as a component of income tax expense or benefit. To date, there have been no interest or penalties charged in relation to the unrecognized tax benefits.

Net Loss per Share

Basic net loss per share is calculated by dividing the net loss by the weighted average number of shares of common stock outstanding during the period without consideration of common stock equivalents. Since the Company was in a loss position for all periods presented, basic net loss per share is the same as diluted net loss per share for all periods as the inclusion of all potential common shares outstanding would have been anti-dilutive.

Recent Accounting Pronouncements

Recently Adopted Accounting Guidance

In August 2018, the FASB issued ASU 2018-13*, Fair Value Measurement (Topic 820): Disclosure Framework-Changes to the Disclosure Requirements for Fair Value Measurement*, which modifies the disclosure requirements on fair value measurements. This guidance is effective for fiscal years beginning after December 15, 2019, and interim periods therein. The Company adopted this guidance effective January 1, 2020. The adoption of this guidance did not have a significant impact on the Company's disclosures.

In November 2018, the FASB issued ASU 2018-18—*Collaborative Arrangements (Topic 808): Clarifying the Interaction between Topic 808 and Topic 606,* or ASU 2018-18. This standard provides guidance on the interaction between Revenue Recognition (Topic 606) and Collaborative Arrangements (Topic 808) by aligning the unit of account guidance between the two topics and

clarifying whether certain transactions between collaborative participants should be accounted for as revenue under Topic 606. ASU 2018-18 is effective for fiscal years beginning after December 15, 2019, and interim periods within those fiscal years. Early adoption is permitted. The Company adopted this guidance effective on January 1, 2020. The adoption did not have a significant impact on the Company's financial statements and related disclosures.

In August 2018, the FASB issued ASU No. 2018-15, *Customer's Accounting for Implementation Costs Incurred in a Cloud Computing Arrangement that is a Service Contract,* or ASU 2018-15. ASU 2018-15 requires a customer in a cloud computing arrangement that is a service contract to follow the internal-use software guidance in ASC 350-40, *Intangibles—Goodwill and Other—Internal Use Software*, or ASC 350-40, to determine which implementation costs to capitalize as assets or expense as incurred. The internal-use software guidance in ASC 350-40 requires that certain costs incurred during the application development stage be capitalized and other costs incurred during the preliminary project and post-implementation stages be expensed as they are incurred. A customer's accounting for the hosting component of the arrangement is not affected by this guidance. The amendments in ASU 2018-15 are effective for fiscal years beginning after December 15, 2019, with early adoption permitted. The Company adopted ASU 2018-15 on a prospective basis in the first quarter of 2020 and the adoption of this standard did not have a material impact on the Company's financial position or results of operations.

Accounting Guidance Not Yet Adopted

In June 2016, the FASB issued ASU No. 2016-13, *Financial Instruments-Credit Losses (Topic 326): Measurement of Credit Losses on Financial Instruments,* or ASU 2016-13. The updated accounting guidance requires changes to the recognition of credit losses on financial instruments not accounted for at fair value through net income. In May 2019, the FASB issued ASU No. 2019-05, *Targeted Transition Relief*, which provides transition guidance to entities that elect the fair value option for eligible instruments. In November 2019, the FASB issued ASU 2019-10 which extends the effective date of the standards for smaller reporting companies to interim and annual periods beginning after December 15, 2022. These standards require using a modified retrospective approach with the cumulative effect recognized as an adjustment to retained earnings. A prospective transition approach is required for debt securities that have recognized an other-than-temporary impairment prior to the effective date. For the Company's receivables from collaborations and certain other financial instruments, the Company will be required to use a forward-looking "expected" credit loss model instead of the existing "incurred" credit loss model, which will generally result in earlier recognition of allowances for credit losses. The Company plans to adopt this standard effective January 1, 2023. The Company is currently evaluating the effect the guidance will have on its financial statements or disclosures.

3. Fair Value Measurements

Fair value accounting is applied for all financial assets and liabilities that are recognized or disclosed at fair value in the consolidated financial statements on a recurring basis (at least annually). Financial instruments include cash and cash equivalents, short-term investments, receivables from collaborations, accounts payable, accrued liabilities and the current portion of deferred revenue that approximate fair value due to their relatively short maturities.

Assets and liabilities recorded at fair value on a recurring basis in the consolidated balance sheets are categorized based upon the level of judgment associated with the inputs used to measure their fair values. Fair value is defined as the exchange price that would be received for an asset or an exit price that would be paid to transfer a liability in the principal or most advantageous market for the asset or liability in an orderly transaction between market participants on the measurement date. The authoritative guidance on fair value measurements establishes a three tier fair value hierarchy for disclosure of fair value measurements as follows:

Level 1—Inputs are unadjusted, quoted prices in active markets for identical assets or liabilities at the measurement date;

Level 2—Inputs are observable, unadjusted quoted prices in active markets for similar assets or liabilities, unadjusted quoted prices for identical or similar assets or liabilities in markets that are not active, or other inputs that are observable or can be corroborated by observable market data for substantially the full term of the related assets or liabilities; and

Level 3—Unobservable inputs that are significant to the measurement of the fair value of the assets or liabilities that are supported by little or no market data.

A financial instrument's categorization within the valuation hierarchy is based upon the lowest level of input that is significant to the fair value measurement. Where quoted prices are available in an active market, securities are classified as Level 1. The Company classifies money market funds as Level 1. When quoted market prices are not available for the specific security, then the Company estimates fair value by using quoted prices for identical or similar instruments in markets that are not active and model-based valuation techniques for which all significant inputs are observable in the market or can be corroborated by observable market data for substantially the full term of the assets. Where applicable, these models project future cash flows and discount the future amounts to a present value using market-based observable inputs obtained from various third party data providers, including but not limited to, benchmark yields, interest rate curves, reported trades, broker/dealer quotes and market reference data. The Company classifies its corporate notes and commercial paper, U.S. treasury securities, and U.S. government agency securities as Level 2. Level 2 inputs for the valuations are limited to quoted prices for similar assets or liabilities in active markets and inputs other than quoted prices that are observable for the asset or liability. There were no transfers between Level 1 and Level 2 during the periods presented.

The following table sets forth the fair value of the Company's financial assets and liabilities, allocated into Level 1, Level 2 and Level 3, that was measured on a recurring basis (in thousands):

	December 31, 2020			
	Level 1	Level 2	Level 3	Total
Financial Assets:				
Money market funds	$ 106,782	$ —	$ —	$ 106,782
Corporate notes and commercial paper	—	6,502	—	6,502
U.S. government agency securities	—	1,503	—	1,503
Total financial assets	$ 106,782	$ 8,005	$ —	$ 114,787

	December 31, 2019			
	Level 1	Level 2	Level 3	Total
Financial Assets:				
Money market funds	$ 45,743	$ —	$ —	$ 45,743
Corporate notes and commercial paper	—	55,770	—	55,770
U.S. treasury securities	—	38,739	—	38,739
U.S. government agency securities	—	16,603	—	16,603
Total financial assets	$ 45,743	$ 111,112	$ —	$ 156,855

4. Balance Sheet Components

Financial Instruments

Cash equivalents and investments, all of which are classified as available-for-sale securities, and restricted cash consisted of the following (in thousands):

	December 31, 2020				December 31, 2019			
	Cost	Unrealized Gain	Unrealized (Loss)	Estimated Fair Value	Cost	Unrealized Gain	Unrealized (Loss)	Estimated Fair Value
Money market funds	$106,782	$ —	$ —	$ 106,782	$ 45,743	$ —	$ —	$ 45,743
Corporate notes and commercial paper	6,501	1	—	6,502	55,761	13	(4)	55,770
U.S. treasury securities	—	—	—	—	38,710	29	—	38,739
U.S. government agency securities	1,501	2	—	1,503	16,599	4	—	16,603
	$114,784	$ 3	$ —	$ 114,787	$156,813	$ 46	$ (4)	$ 156,855
Classified as:								
Cash equivalents				$ 106,342				$ 59,491
Short-term investments				8,005				96,924
Restricted cash				440				440
Total cash equivalents, restricted cash and investments				$ 114,787				$ 156,855

At December 31, 2020, the remaining contractual maturities of available-for-sale securities were less than one year. There have been no significant realized gains or losses on available-for-sale securities for the periods presented. As of December 31, 2020, there were no unrealized losses on cash equivalents and investments. As of December 31, 2020, the Company had a total of $115.6 million in cash, cash equivalents, restricted cash and investments, which included $0.8 million in cash and $114.8 million in cash equivalents, restricted cash and investments.

Property and Equipment, Net

Property and equipment, net consist of the following (in thousands):

	December 31,	
	2020	2019
Research and development equipment	$ 2,174	$ 2,112
Furniture and office equipment	167	167
Computer equipment	448	601
Software	80	80
Leasehold improvements	1,234	1,234
Total property and equipment	4,103	4,194
Less: accumulated depreciation	(3,413)	(3,202)
Property and equipment, net	$ 690	$ 992

Property and equipment depreciation expense for the years ended December 31, 2020, 2019, and 2018 was $364,000, $479,000, and $505,000, respectively.

Accrued and Other Liabilities

Accrued and other liabilities consist of the following (in thousands):

	December 31,	
	2020	2019
Accrued clinical and manufacturing expenses	$ 7,910	$ 8,270
Accrued payroll and related expenses	5,142	5,045
Collaboration reimbursement advances	—	1,547
Current portion of lease liability	1,903	1,478
Other	1,452	1,232
Total accrued and other liabilities	$ 16,407	$ 17,572

5. Commitments and Contingencies

Facilities Lease

On January 1, 2019, the Company adopted ASU 842, which requires leases with a duration greater than twelve months to be recognized on the balance sheet. The Company adopted the standard using the modified retrospective approach with an effective date as of the beginning of the Company's fiscal year, January 1, 2019. Prior period financial information was not recast under the new standard, and therefore, those amounts are not presented below. The Company elected the package of transition provisions available for expired or existing contracts, which allowed it to carryforward its historical assessments of 1) whether contracts are or contain leases, 2) lease classification and 3) initial direct costs. The Company also elected the hindsight practical expedient, and elected to not separate lease and non-lease components.

The Company has a non-cancelable facility lease agreement, or the Lease, for office and laboratory facilities in South San Francisco, California, with a remaining lease term of 3.1 years, through January 2024, and a two-year renewal option prior to expiration. The renewal option to extend the Lease was not considered in the determination of the right-of-use asset or the lease liability for the Lease as the Company did not consider it reasonably certain that it would exercise any such option. The Lease has rent escalation clauses through the lease term and provided for tenant improvement allowances up to $499,900, which were fully utilized by December 2017 and included in the calculation of the lease liability. The Lease provides that the Company is obligated to pay certain variable costs, including taxes and operating expenses. The Lease is classified as an operating lease. The Company has measured the present value of its lease liability using an estimated incremental borrowing rate of 9%. In addition, the Company had a non-cancelable sublease agreement for a portion of its facilities through February 2020. The sublease agreement provided that the subtenant is obligated to pay its share of the variable costs under the Lease.

The components of net operating lease costs included in the consolidated statement of operations for the year December 31, 2020 and 2019, were as follows (in thousands):

	Year Ended December 31,	
Operating Lease Costs:	2020	2019
Straight-line rent expense related to facility operating lease	$ 2,177	$ 2,177
Variable rent expense related to operating lease	1,509	1,327
Sublease income	(187)	(1,115)
Variable sublease income	(93)	(509)
Net operating lease costs	$ 3,406	$ 1,880

Cash paid for amounts included in the measurement of the lease liabilities for the year ended December 31, 2020 and 2019, was $2.1 million and $2.3 million, respectively, and was included in net cash used in operating activities in the Company's consolidated statements of cash flows.

Supplemental balance sheet information related to the Company's operating lease were as follows as of December 31 (in thousands):

	December 31,	
Operating Lease Liability:	**2020**	**2019**
Current portion included in accrued and other liabilities	$ 1,903	$ 1,478
Noncurrent operating lease liability	4,815	6,718
Total operating lease liability	$ 6,718	$ 8,196

The maturities of the Company's lease liability as of December 31, 2020, were as follows (in thousands):

Year ending December 31:	
2021	$ 2,413
2022	2,485
2023	2,559
2024	219
Total lease payments	7,676
Less: interest	(958)
Present value of lease liability	$ 6,718

The Company has an existing letter of credit of $440,000 as a security deposit to the lease. The lessor shall be entitled to draw on the letter of credit in the event of any uncured default by the Company under the terms of the lease.

Expenses and income associated with the Company's operating leases were as follows (in thousands):

	Year Ended December 31,		
	2020	**2019**	**2018**
Rent expense	$ 3,686	$ 3,504	$ 3,439
Sublease income/gain	(280)	(1,624)	(1,566)

Indemnifications

The Company indemnifies each of its officers and directors for certain events or occurrences, subject to certain limits, while the officer or director is or was serving at the Company's request in such capacity, as permitted under Delaware law and in accordance with its certificate of incorporation and bylaws. The term of the indemnification period lasts as long as an officer or a director may be subject to any proceeding arising out of acts or omissions of such officer or director in such capacity. The maximum amount of potential future indemnification is unlimited; however, the Company currently holds director and officer liability insurance. This insurance allows the transfer of risk associated with the Company's exposure and may enable it to recover a portion of any future amounts paid. The Company believes that the fair value of these indemnification obligations is minimal. Accordingly, it has not recognized any liabilities relating to these obligations for any period presented.

6. Stockholders' Equity

Public Offering

In June 2019, the Company entered into an underwriting agreement with SVB Leerink LLC, Wells Fargo Securities, LLC, and William Blair & Company, LLC (collectively, the 2019 Underwriters), pursuant to which the Company issued and sold 14,375,000 shares of common stock, including 1,875,000 shares sold pursuant to the 2019 Underwriters' exercise in full of their option to purchase additional shares. The price to the public in the offering was $4.00 per share, and the 2019 Underwriters purchased the shares from the Company at a price of $3.76 per share. The net proceeds to the Company from this public offering were approximately $53.8 million, after deducting underwriting discounts and commissions and other offering expenses.

In April 2020, the Company entered into an underwriting agreement with Citigroup Global Markets, Inc., or the Underwriter, pursuant to which the Company issued and sold 5,750,000 shares of common stock, including 750,000 shares sold pursuant to the Underwriter's exercise in full of their option to purchase additional shares. The price to the public in the offering was $6.25 per share, and the Underwriter purchased the shares from the Company at a price of $5.88 per share. The net proceeds to the Company from this public offering were approximately $33.5 million, after deducting underwriting discounts and commissions and other offering expenses.

At-the-Market Offerings

In August 2017, the Company entered into a sales agreement with Cowen and Company LLC, or Cowen, as sales agent and underwriter, pursuant to which the Company could issue and sell shares of its common stock with an aggregate maximum offering price of $50.0 million under an at-the-market offering program, or the 2017 ATM program. The Company paid Cowen up to 3% of gross proceeds for any common stock sold through the sales agreement. In December 2019, the Company terminated its sales agreement with Cowen.

In December 2019, the Company entered into a sales agreement with Jefferies LLC, or Jefferies, as sales agent and underwriter, pursuant to which the Company could issue and sell shares of its common stock with an aggregate maximum offering price of $50.0 million under an at-the-market offering program, or the 2019 Jefferies ATM program. The Company will pay Jefferies up to 3% of gross proceeds for any common stock sold through the sales agreement. During the three months ended March 31, 2020, the Company sold an aggregate of 1,160,425 shares at an average price of approximately $6.51 per share for gross proceeds of $7.6 million, resulting in net proceeds of $7.4 million after underwriting fees and offering expenses. As of March 31, 2020, the Company had sold all available shares under the 2019 ATM program.

In March 2020, the Company entered into a sales agreement with Jefferies as sales agent and underwriter, pursuant to which the Company could issue and sell shares of its common stock with an aggregate maximum offering price of $50.0 million under an at-the-market offering program, or the March 2020 ATM. In August 2020, in connection with its S-3 filing, the Company entered into a new sales agreement with Jefferies for $75.0 million, or the August 2020 ATM, and the March 2020 ATM was terminated. The Company will pay Jefferies up to 3% of gross proceeds for any common stock sold through the sales agreement. As of December 31, 2020, no shares had been sold under these ATM programs.

7. Equity Incentive Plans

2010 Plan

In 2010, the Company adopted the 2010 Equity Incentive Plan, or the 2010 Plan. Under the 2010 Plan, shares of the Company's common stock have been reserved for the issuance of stock options to employees, directors, and consultants under terms and provisions established by the Board of Directors. Under the terms of the 2010 Plan, options were granted at an exercise price not less than fair market value. For employees holding more than 10% of the voting rights of all classes of stock, the exercise prices for incentive and nonstatutory stock options were not less than 110% of fair market value, as determined by the Board of Directors. The terms of options granted under the 2010 Plan did not exceed ten years. The vesting schedule of option grants was typically four years. The Company granted options under the 2010 Plan until October 2014 when it was terminated as to future awards, although it continues to govern the terms of options that remain outstanding under the 2010 Plan. As of December 31, 2020, approximately 483,000 shares of common stock are subject to options outstanding under the 2010 Plan.

2014 Plan

In September 2014, the Company's Board of Directors and stockholders approved the 2014 Equity Incentive Plan, or the 2014 Plan, which became effective in October 2014, at which time the 2010 Plan was terminated. The 2014 Plan provides for the grant of stock options, other forms of equity compensation, and performance cash awards. The number of shares of common stock reserved for issuance under the 2014 Plan will automatically increase on January 1 of each year, beginning on January 1, 2015 and ending on and including January 1, 2024, by 4% of the total number of shares of the Company's capital stock outstanding on December 31 of the preceding calendar year, or a lesser number of shares determined by the Company's Board of Directors.

As of December 31, 2020, approximately 8.8 million shares of common stock were reserved for issuance under the 2014 Plan and there were approximately 771,000 shares of common stock available for future grant. The Company issues new shares upon the exercise of options. The maximum term of options granted under the 2014 Plan is ten years. The vesting schedule of option grants are typically four years.

2018 Inducement Plan

In January 2018, the Company's Board of Directors approved the 2018 Inducement Plan, a non-stockholder approved stock plan, in order to award nonstatutory options and restricted stock unit awards to persons not previously an employee or director of the Company, or following a bona fide period of non-employment, as an inducement material to such persons entering into employment with the Company. As of December 31, 2020, there were 1 million shares reserved for issuance under the 2018 Inducement Plan and there were approximately 624,000 shares of common stock available for future grant. The maximum term of options granted under the 2018 Inducement Plan is ten years. The vesting schedule of option grants are typically four years.

The following summarizes option activity (in thousands, except price per option data):

	Options Outstanding		
	Number of Options	Weighted-Average Exercise Price per Option	Aggregate Intrinsic Value
Outstanding — December 31, 2019	6,513	$ 6.89	$ 5,808
Options granted	2,617	$ 6.88	
Options exercised	(64)	$ 3.10	
Options cancelled	(429)	$ 7.00	
Outstanding — December 31, 2020	8,637	$ 6.91	$ 2,758
Exercisable — December 31, 2020	4,979	$ 7.24	$ 2,232
Vested and expected to vest — December 31, 2020	8,637	$ 6.91	$ 2,758

The aggregate intrinsic values of options outstanding, exercisable, vested and expected to vest were calculated as the difference between the exercise price of the options and the fair value of the Company's common stock of $4.91 per share as of December 31, 2020.

The weighted-average fair value per share of employee options granted during the years ended December 31, 2020, 2019, and 2018 were $5.09, $3.46, and $5.69, respectively. The total fair value of options that vested during the years ended December 31, 2020, 2019, 2018 was $6.9 million, $6.7 million, and $5.6 million, respectively. The aggregate intrinsic value of options exercised was $0.2 million, $0.3 million, and $0.6 million for the years ended December 31, 2020, 2019, and 2018, respectively.

As of December 31, 2020, the weighted-average remaining contractual life was 5.32 years and 6.40 years for exercisable options and vested and expected to vest options, respectively.

Stock-Based Compensation Expense

Total stock-based compensation recognized related to the 2010 Plan, 2014 Plan and 2018 Inducement Plan was as follows (in thousands):

	Year Ended December, 31		
	2020	2019	2018
Research and development	$ 3,742	$ 3,223	$ 3,187
General and administrative	3,867	2,886	3,233
Total stock-based compensation	$ 7,609	$ 6,109	$ 6,420

As of December 31, 2020, the total unrecognized compensation expense related to unvested options was $14.6 million, which the Company expects to recognize over an estimated weighted average period of 2.53 years.

In each of the periods presented, the exercise price per share for each stock option was the same as the fair value of the Company's common stock on the date of grant.

In determining the fair value of the stock-based awards, the Company uses the Black-Scholes option-pricing model and assumptions discussed below. Each of these inputs is subjective and generally requires significant judgment to determine.

Expected Term—The Company's expected term represents the period that the Company's stock-based awards are expected to be outstanding and is determined using the simplified method (based on the midpoint between the vesting date and the end of the contractual term).

Expected Volatility—The expected volatility was estimated based on a weighted volatility using both the Company's trading history for its common stock and 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—The Company has never paid dividends on its common stock and has no plans to pay dividends on its common stock. Therefore, the Company used an expected dividend yield of zero.

The fair value of stock option awards was estimated using a Black-Scholes option pricing model with the following assumptions:

	Year Ended December 31,		
	2020	2019	2018
Expected term	5.3 - 6.1 years	5.3 - 6.1 years	5.3 - 6.1 years
Volatility	85.2% - 89.8%	84.6% - 85.7%	84.4% - 95.7%
Risk-free interest rate	0.31% - 1.69%	1.42% - 2.60%	2.40% - 3.10%
Expected dividend rate	—%	—%	—%

ESPP

In September 2014, the Company's Board of Directors and stockholders approved the 2014 Employee Stock Purchase Plan, or the ESPP, which became effective in October 2014. The number of shares of common stock reserved for issuance under the ESPP will increase automatically each year, beginning on January 1, 2015 and continuing through and including January 1, 2024, by the lesser of (1) 1% of the total number of shares of common stock outstanding on December 31 of the preceding calendar year; (2) 250,000 shares of common stock; or (3) such lesser number as determined by the Company's Board of Directors.

The ESPP allows eligible employees to purchase shares of the Company's common stock at a discount through payroll deductions of up to 15% of their eligible compensation, subject to certain plan limitations. Through December 9, 2018, the ESPP provided for 24-month offering periods with four 6-month purchase periods, and at the end of each purchase period, employees were able to purchase shares at 85% of the lower of the fair market value of the Company's common stock on the first trading day of the offering period or on the last day of the purchase period. Effective beginning December 10, 2018, the ESPP provides for 6-month offering periods and a 6-month purchase period, and at the end of each purchase period, employees are able to purchase shares at 85% of the lower of the fair market value of the Company's common stock on the first trading day of the offering period or on the last day of the purchase period. As of December 31, 2020, 960,522 shares of common stock have been issued to employees participating in the ESPP and 556,128 shares were available for issuance under the ESPP. The ESPP is a compensatory plan as defined by the authoritative guidance for stock compensation. As such stock-based compensation expense has been recorded for the years ended December 31, 2020, 2019, and 2018.

Total stock-based compensation expense recognized related to the ESPP was as follows (in thousands):

	Year Ended December 31,		
	2020	2019	2018
Research and development	$ 343	$ 269	$ 819
General and administrative	108	88	198
Total stock-based compensation	$ 451	$ 357	$ 1,017

The Company used the following assumptions to estimate the fair value of stock offered under the ESPP for the years ended December 31, 2020, 2019, and 2018:

	Year Ended December 31,		
	2020	2019	2018
Expected term	0.24 - 0.50 years	0.24 - 0.50 years	0.24 - 0.86 years
Volatility	54.3% - 125.5 %	52.9% - 82.0 %	61.0% - 86.6%
Risk-free interest rate	0.08% - 1.59%	1.58% - 2.55%	1.56% - 2.55%
Expected dividend rate	—%	—%	—%

8. Employee Benefit Plan

The Company has an employee benefit plan under Section 401(k) of the Internal Revenue Code. The plan allows employees to contribute a portion of their compensation, subject to certain limitations. The Company may make contributions to this plan at its discretion. For the year ended December, 31, 2020 and 2019, the Company matched a portion of the employees' contributions up to a defined maximum, and recognized expense of approximately $0.4 million and $0.3 million, respectively relating to these contributions. No contributions were made by the Company to the plan for the year ended December 31, 2018.

9. Income Taxes

No provision for income taxes was recorded for the years ended December 31, 2020, 2019, and 2018. The Company has incurred net operating losses for all the periods presented. The Company has not reflected any benefit of such net operating loss carryforwards in the accompanying consolidated financial statements.

The domestic and foreign components of loss before provision for income tax are as follows (in thousands*):*

	Year Ended December 31,		
	2020	2019	2018
Domestic	$ (90,137)	$ (89,860)	$ (54,629)
Foreign	—	—	—
Total	$ (90,137)	$ (89,860)	$ (54,629)

The effective tax rate of the provision for income taxes differs from the federal statutory rate as follows:

	Year Ended December, 31		
	2020	2019	2018
Federal statutory income tax rate	21.0%	21.0%	21.0%
State income taxes, net of federal benefit	—	—	0.7
Federal and state tax credits, net of reserves	2.7	2.5	4.4
Stock-based compensation	(0.7)	(0.4)	(1.4)
Other permanent differences	(0.1)	(0.1)	(0.1)
Change in valuation allowance	(22.9)	(23.0)	(24.6)
	0%	0%	0%

The components of the deferred tax assets and liability are as follows (in thousands):

	Year Ended December 31,	
	2020	2019
Deferred tax assets:		
Net operating loss carryforwards	$ 73,405	$ 55,531
Tax credits, net of reserves	11,874	9,514
Accrued liabilities	948	1,600
Stock-based compensation	4,091	3,070
Operating lease liability	1,411	1,721
Other	277	279
Gross deferred tax assets	92,006	71,715
Valuation allowance	(90,797)	(70,190)
Total deferred tax assets	1,209	1,525
Deferred tax liability:		
Operating lease right-of-use asset	(1,209)	(1,525)
Total deferred tax liability	(1,209)	(1,525)
Net deferred tax assets (liability)	$ —	$ —

Realization of the Company’s deferred tax assets is dependent upon the Company generating future taxable income, the timing and amount of which are uncertain. Accordingly, the deferred tax assets have been fully offset by a valuation allowance as of December 31, 2020 and 2019. The valuation allowance increased by $20.6 million for the year ended December 31, 2020, and increased by $20.7 million for the year ended December 31, 2019. ASC Topic 740 requires that the tax benefit of deductible temporary differences of carryforwards be recorded as a deferred tax asset to the extent that management assesses that realization is "more likely than not." Future realization of the tax benefit ultimately depends on the existence of sufficient taxable income within the carryback or carryforward period available under the tax law. The Company has set up the valuation allowance against the federal and state deferred tax assets because based on all available evidence, these deferred tax assets are not more likely than not to be realizable.

As of December 31, 2020 and 2019, the Company had approximately $332.5 million and $247.4 million of federal operating loss carryforwards, respectively, and $53.7 million and $53.5 million of state net operating loss carryforwards, respectively, available to reduce future taxable income. Of the federal net operating loss carryforwards, $129.3 million will begin to expire in 2030, and $203.2 million will carryforward indefinitely, while state net operating losses begin to expire in 2030.

As of December 31, 2020 and 2019, the Company also had research and development tax credit carryforwards of approximately $13.4 million and $10.7 million for federal purposes, respectively, and $6.3 million and $5.1 million for state purposes, respectively, 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.

Sections 382 and 383 place a limitation on the amount of taxable income which can be offset by carryforward tax attributes, such as net operating losses or tax credits, after a change in control. Generally, after a change in control, a loss corporation cannot deduct carryforward tax attributes in excess of the limitation prescribed by Section 382 and 383. Therefore, certain of the Company's carryforward tax attributes may be subject to an annual limitation regarding their utilization against taxable income in future periods. As a result of the Company's IPO in 2014, the Company triggered an "ownership change" as defined in Internal Revenue Code Section 382 and related provisions. Additionally, due to stock acquired by investors and reported under Section 13(g), the Company believes that an “ownership change” occurred during 2018, as well. The Company believes that some of its net operating losses and credit carryforwards may be limited by these ownership changes but that any limitation would not have a significant impact to the financial statements since there is no utilization of the net operating losses and credit carryforwards and a full valuation allowance exists against the net operating losses and credit carryforwards for U.S. tax purposes. Subsequent ownership changes since 2018 may subject the Company to annual limitations of its net operating loss and credit carryforwards. Such annual limitation could result in the expiration of the net operating loss and credit carryforwards before utilization.

U.S. tax law subjects a U.S. shareholder to current tax on global intangible low-taxed income (GILTI) earned by certain foreign subsidiaries. The FASB Staff Q&A, Topic 740 No. 5, *Accounting for Global Intangible Low-Taxed Income*, states that an entity can make an accounting policy election to either recognize deferred taxes for temporary differences expected to reverse as GILTI in future years or provide for the tax expense related to GILTI in the year the tax is incurred. The Company has elected to recognize the tax on

GILTI as a period expense in the period the tax is incurred. As a result of no activity in the Company's dormant foreign subsidiaries, the Company has no GILTI inclusion for the year ended 2020, 2019 and 2018.

On March 11, 2020, the World Health Organization declared the novel strain of coronavirus (COVID-19) a global pandemic and recommended containment and mitigation measures worldwide. The Coronavirus Aid, Relief, and Economic Security Act (CARES Act) was enacted in the US on March 27, 2020, which contains several provisions, including, but not limited to, changes to the rules governing net operating losses (NOLs) and technical corrections to certain provisions in the 2017 tax law ("Tax Cuts and Jobs Act"). Since the Company has historical tax losses and records a full valuation allowance against its US deferred tax assets, the impact of these changes was limited to the timing of the availability of its NOLs.

Uncertain Tax Positions

As of December 31, 2020, the Company's total unrecognized tax benefit was $7.3 million, of which none of the tax benefit, if recognized, would affect the effective income tax rate due to the valuation allowance that currently offsets deferred tax assets. A reconciliation of the Company's unrecognized tax benefits for the years ended December 31, 2020, 2019, and 2018 is as follows (in thousands):

	Year Ended December 31,		
	2020	2019	2018
Balance at beginning of year	$ 5,993	$ 4,964	$ 3,623
Decreases related to prior year tax positions	(24)	(6)	—
Additions based on tax positions related to current year	1,303	1,035	1,341
Balance at end of year	$ 7,272	$ 5,993	$ 4,964

The unrecognized tax benefits, if recognized and in the absence of a full valuation allowance, would increase the Company's credit carryforwards and hence deferred tax assets. The Company does not expect the unrecognized tax benefits to change significantly over the next 12 months.

Interest and penalties are zero, and the Company's policy is to account for interest and penalties in tax expense on the statement of operations. The Company files income tax returns in the U.S. federal, California and various other state tax jurisdictions. All periods since inception are subject to examination by U.S. federal, California and other state tax jurisdictions, none of which are currently under examination.

10. Net Loss per Common Share

Since the Company was in a loss position for all periods presented, diluted net loss per share is the same as basic net loss per share for all periods as the inclusion of all potential common shares outstanding would have been anti-dilutive.

Potentially dilutive securities that were not included in the diluted per share calculations because they would be anti-dilutive were as follows (in thousands):

	December 31,		
	2020	2019	2018
Options to purchase common stock	8,637	6,513	4,669
Employee stock plan purchases	21	19	16
Total	8,658	6,532	4,685

11. Licensing and Collaboration Agreements

Incyte Collaboration and License Agreement

On January 27, 2017, the Company entered into a collaboration and license agreement with Incyte, or the Incyte Collaboration Agreement. Under the terms of the Incyte Collaboration Agreement, the Company granted Incyte an exclusive, worldwide license to develop and commercialize its small molecule arginase inhibitors for hematology and oncology indications. Through September 30,

2020, the parties collaborated on and co-funded the development of the licensed products, with Incyte bearing 70% and the Company bearing 30% of global development costs. The parties would share profits and losses in the United States, with 60% to Incyte and 40% to the Company. The Company would have the right to co-detail the licensed products in the United States, and Incyte will pay the Company tiered royalties ranging from the low to mid-double digits on net sales of licensed products outside the United States.

The Incyte Collaboration Agreement also provides that the Company may choose to opt out of its co-funding obligations at any time. On August 28, 2020, the Company delivered written notice to Incyte of its decision to opt out of its co-development rights effective September 30, 2020. As a result of the Company's decision to opt out, Incyte will pay all costs to develop INCB001158 or any other licensed products. In addition, the Company's rights to U.S. profit sharing will no longer be in effect, and instead Incyte will pay Calithera tiered royalties ranging from the low double digits to mid-teens on net sales of licensed products in the U.S., an incremental 3% royalty on annual net sales in the United States of such licensed product until such incremental royalty equals 120% of previous development expenditures incurred by the Company.

Under the Incyte Collaboration Agreement, the Company received an upfront payment of $45.0 million in February 2017. In March 2017, the Company achieved a development milestone of $12.0 million, for which the Company received payment in May of 2017. In April 2020, the Company filed a complaint against Incyte in the Superior Court of California, San Francisco County, asserting claims for breach of contract arising out of Incyte's failure to pay two milestone payments the Company believes are due under the Collaboration Agreement. As of December 31, 2020, no revenue has been recognized for these two milestones as the collectability remains uncertain. Total remaining potential development, regulatory and commercialization milestones as of December 31, 2020 were $738.0 million.

The Incyte Collaboration Agreement is considered to be under the scope of ASC Topic 808, *Collaborative Arrangements*. The Company has concluded that the research and development co-funding activities were not representative of a customer relationship and this unit of account is accounted for as an increase to or reduction of research and development expenses, rather than as revenue. In addition, the Company has analogized to ASC 606 for other aspects of the arrangement. The performance obligations under the Incyte Collaboration Agreement consist of intellectual property licenses and the performance of certain manufacturing and manufacturing technology transfer services. The Company determined that the license is not distinct from the associated manufacturing and technology transfer services to be performed under the agreement. Specifically, the Company believes the license is not capable of being distinct, as Incyte did not have the know-how to manufacture the collaboration product without Calithera's assistance until completion of the manufacturing technology transfer process, and no other third parties could perform such assistance due to the early stage nature of the licensed intellectual property as well as Calithera's propriety knowledge with respect to the licensed intellectual property.

The Company adopted ASC 606 on January 1, 2018 under the modified retrospective approach. In accordance with ASC 606, the Company determined the transaction price of the Incyte Collaboration Agreement to be $57.0 million, representing the $45.0 million upfront payment and the $12.0 million developmental milestone payment from Incyte that was earned in March 2017. The $57.0 million transaction price was recognized over the estimated performance period, based on the measure of progress toward completion for the combined performance obligation, which was satisfied as of June 2018. The measure of progress towards completion was based on the effort of certain employees within the Company who dedicated time to complete the manufacturing services and technology transfer to Incyte. An $8.8 million cumulative effect adjustment to decrease the accumulated deficit and deferred revenue was recorded on January 1, 2018, as a result of applying the new standard. As of June 30, 2018, the manufacturing services and technology transfer to Incyte were determined to be substantially complete. For the year ended December 31, 2018, the Company recognized revenue from its collaboration with Incyte totaling $22.2 million related to the completion of the combined performance obligation. No revenue was recognized during the year ended December 31, 2020 and 2019, related to the Incyte Collaboration Agreement.

Net costs associated with co-development activities performed under the Incyte Collaboration Agreement are included in research and development expenses in the accompanying consolidated statements of operations, with any reimbursement of costs by Incyte reflected as a reduction of such expenses. For the years ended December 31, 2020, 2019, and 2018, net costs (payable to) reimbursable by Incyte were $8,000, ($0.2) million, and $3.9 million, respectively. As of December 31, 2020, the receivable due from Incyte was $0.9 million.

Bristol-Myers Squibb and Pfizer Collaboration Agreements

In December 2016, the Company entered into a clinical trial collaboration and supply agreement with Bristol-Myers Squibb, or BMS, to evaluate BMS's PD-1 inhibitor nivolumab (OPDIVO®) in combination with telaglenastat. In November 2017, the agreement was expanded such that certain development costs would be shared. In July 2019, with the enrollment on the trial complete, the collaboration with Bristol-Myers was discontinued.

In October 2018, the Company entered into a clinical trial collaboration and supply agreement with Pfizer to evaluate Pfizer's PARP inhibitor talazoparib (Talzenna) and CDK4/6 inhibitor palbociclib (Ibrance), each in combination with telaglenastat.

Under the terms of the clinical collaborations, BMS and Pfizer each provide reimbursement of certain development costs. Costs associated with development activities performed under the clinical collaborations are included in research and development expenses in the accompanying consolidated statements of operations, with any reimbursements of costs reflected as a reduction of such expenses. For the years ended December 31, 2020, 2019 and 2018, net costs from BMS were not material to the consolidated financial statements. For the year ended December 31, 2020, net costs from Pfizer recognized as a reduction to research and development expenses were $1.5 million. For the years ended December 31, 2019 and 2018, net costs from Pfizer were not material to the consolidated financial statements.

S*ymbioscience License Agreement*

In December 2014, the Company entered into an exclusive license agreement with Mars, Inc., by and through its Mars Symbioscience division, or Symbioscience, under which the Company has been granted the exclusive, worldwide license rights to develop and commercialize Symbioscience's portfolio of arginase inhibitors for use in human healthcare, or the Symbioscience License Agreement. No expenses were recognized related to its licensing arrangement with Mars Symbioscience for the year ended December 31, 2020, 2019, and 2018.

The Company may make future payments of up to $23.6 million contingent upon attainment of various development and regulatory milestones and $95.0 million contingent upon attainment of various sales milestones. Additionally, the Company will pay royalties on sales of the licensed product, if such product sales are ever achieved. If the Company develops additional licensed products, after achieving regulatory approval of the first licensed product, the Company would owe additional regulatory milestone payments and additional royalty payments based on sales of such additional licensed products.

12. Cystic Fibrosis Foundation Development Award

In October 2020, the Company was awarded $2.4 million from the Cystic Fibrosis Foundation, or CFF, to support the clinical development of CB-280 in cystic fibrosis. The award will be paid in installments upon the achievement of certain milestones. The Company recognizes the CFF milestones awards as a reduction to research and development expenses in the accompanying consolidated statements of operations in the period the milestone is achieved and expenses have been incurred. For the year ended December 31, 2020, amounts from the CFF recognized as a reduction of research and development expenses was $0.6 million.

The award contains provisions where the Company must repay up to two times the award if it ceases to use commercially reasonable efforts to develop CB-280. Upon commercialization, the Company will owe certain royalty payments to the CFF up to a royalty cap. The Company may also be obligated to make a payment to CFF if the Company transfers, sells or licenses a product in the cystic fibrosis field, or if the Company enters into a change of control transaction.

13. Subsequent Events

Reduction in Workforce

On January 4, 2021, the Company announced a plan to reduce its workforce by approximately 35%. The Company anticipates the one-time, cash severance-related charge associated with the workforce reduction to be approximately $1.1 million to $1.2 million, with the majority to be completed by the end of the first quarter of 2021.

Lease Amendment

In March 2021, the Company amended its lease to reduce its rentable area from approximately 54,000 square feet to approximately 34,000 square feet. The related reduction in rent was effective January 1, 2021. In connection with the amendment, the Company will also reduce its existing letter of credit from $440,000 to $270,000 as a security deposit to the lease.

Item 9. Changes in and Disagreements With Accountants on Accounting and Financial Disclosure.

None.

Item 9A. Controls and Procedures.

Evaluation of Disclosure Controls and Procedures

As of December 31, 2020, management, with the participation of our Chief Executive Officer and Chief Financial Officer, performed an evaluation of the effectiveness of the design and operation of our disclosure controls and procedures as defined in Rules 13a-15(e) and 15d-15(e) of the Exchange Act. Our disclosure controls and procedures are designed to ensure that information required to be disclosed in the reports we file or submit under the Exchange Act is recorded, processed, summarized and reported within the time periods specified in the Securities and Exchange Commission's rules and forms, and that such information is accumulated and communicated to our management, including the Chief Executive Officer and Chief Financial Officer, to allow timely decisions regarding required disclosures.

Any controls and procedures, no matter how well designed and operated, can provide only reasonable assurance of achieving the desired control objective and management necessarily applies its judgment in evaluating the cost-benefit relationship of possible controls and procedures. Based on this evaluation, our Chief Executive Officer and our Chief Financial Officer concluded that, as of December 31, 2020, the design and operation of our disclosure controls and procedures were effective at a reasonable assurance level.

Management's Report on Internal Control Over Financial Reporting

Our management is responsible for establishing and maintaining adequate internal control over financial reporting, as such term is defined in Exchange Act Rules 13a-15(f) and 15d-15(f). Our management conducted an evaluation of the effectiveness of our internal control over financial reporting as of December 31, 2020 based on the criteria established in *Internal Control - Integrated Framework (2013)* issued by the Committee of Sponsoring Organizations of the Treadway Commission.

Based on the results of its evaluation, management concluded that our internal control over financial reporting was effective as of December 31, 2020.

Limitations on Effectiveness of Controls and Procedures and Internal Control over Financial Reporting

In designing and evaluating the disclosure controls and procedures and internal control over financial reporting, management recognizes that any controls and procedures, no matter how well designed and operated, can provide only reasonable assurance of achieving the desired control objectives. In addition, the design of disclosure controls and procedures and internal control over financial reporting must reflect the fact that there are resource constraints and that management is required to apply judgment in evaluating the benefits of possible controls and procedures relative to their costs.

Changes in Internal Control over Financial Reporting

There was no change in our internal control over financial reporting during the three months ended December 31, 2020 that has materially affected, or is reasonably likely to materially affect, our internal control over financial reporting.

Item 9B. Other Information.

None.

PART III

Item 10. Directors, Executive Officers and Corporate Governance.

Information required by this item will be contained in our definitive proxy statement to be filed with the Securities and Exchange Commission on Schedule 14A in connection with our 2021 Annual Meeting of Stockholders or the Proxy Statement, which is expected to be filed not later than 120 days after the end of our year ended December 31, 2020, under the headings "Executive Officers," "Election of Directors," and "Information Regarding the Board of Directors and Corporate Governance," and is incorporated herein by reference.

We have adopted a Code of Business Conduct and Ethics that applies to our officers, directors and employees, which is available on our website at www.calithera.com. The Code of Business Conduct and Ethics is intended to qualify as a "code of ethics" within the meaning of Section 406 of the Sarbanes-Oxley Act of 2002 and Item 406 of Regulation S-K. In addition, we intend to promptly disclose (1) the nature of any amendment to our Code of Business Conduct and Ethics that applies to our principal executive officer, principal financial officer, principal accounting officer or controller or persons performing similar functions and (2) the nature of any waiver, including an implicit waiver, from a provision of our code of ethics that is granted to one of these specified officers, the name of such person who is granted the waiver and the date of the waiver on our website in the future.

Item 11. Executive Compensation.

The information required by this item regarding executive compensation is incorporated by reference to the information set forth in the section titled "Executive Compensation" in our Proxy Statement.

Item 12. Security Ownership of Certain Beneficial Owners and Management and Related Stockholder Matters.

The information required by this item regarding security ownership of certain beneficial owners and management is incorporated by reference to the information set forth in the section titled "Security Ownership of Certain Beneficial Owners and Management" in our Proxy Statement.

Item 13. Certain Relationships and Related Transactions, and Director Independence.

The information required by this item regarding certain relationships and related transactions and director independence is incorporated by reference to the information set forth in the sections titled "Transactions with Related Parties" and "Election of Directors – Independence of the Board of Directors," respectively, in our Proxy Statement.

Item 14. Principal Accounting Fees and Services.

The information required by this item regarding principal accountant fees and services is incorporated by reference to the information set forth in the section titled "Principal Accountant Fees and Services" in our Proxy Statement.

PART IV

Item 15. Exhibits, Financial Statement Schedules.

(a) The following documents are filed as part of this report:

1. Financial Statements

   See Index to Consolidated Financial Statements at Item 8 herein.

2. Financial Statement Schedules

   All schedules are omitted because they are not applicable or the required information is shown in the financial statements or notes thereto.

3. Exhibits

Exhibit Number	Exhibit Description	Incorporation By Reference			
		Form	SEC File No.	Exhibit	Filing Date
3.1	Amended and Restated Certificate of Incorporation of the Registrant.	8-K	001-36644	3.1	10/07/2014
3.2	Amended and Restated Bylaws of the Registrant.	10-Q	001-36644	3.2	8/10/2020
4.1	Reference is made to Exhibits 3.1 through 3.2.				
4.2	Form of common stock certificate of the Registrant.	S-1	333-198355	4.1	9/25/2014
4.3	Description of Capital Stock.	10-K	001-36644	4.3	3/11/2020
10.1	Amended and Restated Investor Rights Agreement, among the Registrant and certain of its security holders, dated October 7, 2013, as amended.	S-1	333-198355	10.1	8/25/2014
10.2	2014 Equity Incentive Plan, as amended.	8-K	001-36644	99.1	1/26/2021
10.3	Forms of option agreement and option grant notice under the Calithera Biosciences, Inc. 2014 Equity Incentive Plan.	S-1	333-198355	10.5	9/25/2014
10.4	2014 Employee Stock Purchase Plan.	S-1	333-198355	10.6	9/25/2014
10.5	Form of Indemnification Agreement between the Registrant and each of its directors and executive officers.	S-1	333-198355	10.13	9/19/2014
10.6	Lease between Are-Technology Center SSF, LLC and the Registrant, dated February 14, 2013.	S-1	333-198355	10.14	8/25/2014
10.7	Amendment to lease between Are-Technology Center SSF, LLC and the Registrant, dated October 30, 2013.	S-1	333-198355	10.15	8/25/2014
10.8†	Collaboration and License Agreement by and between the Registrant and Mars, Inc., dated December 9, 2014.	10-K	001-36644	10.16	3/27/2015
10.9	Second Amendment to Lease Agreement by and between ARE-Technology Center SSF, LLC and Calithera Biosciences, Inc., effective March 1, 2016.	10-Q	001-36644	10.18	5/10/2016
10.10†	Collaboration and License Agreement between Incyte Corporation and the Registrant, dated January 27, 2017.	10-Q	001-36644	10.1	5/09/2017
10.11	Third Amendment to Lease Agreement between Are-Technology Center SSF, LLC and the Registrant, dated February 28, 2017.	10-Q	001-36644	10.2	5/09/2017
10.12	Calithera Biosciences Inc. Severance Benefit Plan.	10-Q	001-36644	10.1	11/02/2017
10.13	2018 Inducement Plan.	S-8	333-223533	99.4	03/08/2018
10.14	Form of Stock Option Grant Notice and Option Agreement under the Calithera Biosciences, Inc. 2018 Inducement Plan.	S-8	333-223533	99.5	03/08/2018
10.15	Form of Restricted Stock Unit Grant Notice and Restricted Stock Unit Award Agreement under the Calithera Biosciences, Inc. 2014 Equity Incentive Plan.	10-Q	001-36644	10.1	11/05/2020
23.1^	Consent of Independent Registered Public Accounting Firm.				
24.1^	Power of Attorney (included on signature page to this Annual Report on Form 10-K).				
31.1^	Certification of Principal Executive Officer pursuant to Rule 13a-14(a).				
31.2^	Certification of Principal Financial and Accounting Officer pursuant to Rule 13a-14(a).				
32.1*^	Certification of Principal Executive Officer pursuant to Rule 13a-14(b) of the Securities Exchange Act of 1934, as amended, and 18 U.S.C. Section 1350, as adopted pursuant to Section 906 of the Sarbanes-Oxley Act of 2002.				

Exhibit Number	Exhibit Description	Incorporation By Reference			
		Form	SEC File No.	Exhibit	Filing Date
32.2*^	Certification of Principal Financial and Accounting Officer pursuant to Rule 13a-14(b) of the Securities Exchange Act of 1934, as amended, and 18 U.S.C. Section 1350, as adopted pursuant to Section 906 of the Sarbanes-Oxley Act of 2002.				
101.INS**	Inline XBRL Instance Document – the instance document does not appear in the Interactive Data File because its XBRL tags are embedded within the Inline XBRL document.				
101.SCH**	Inline XBRL Taxonomy Extension Schema Document.				
101.CAL**	Inline XBRL Taxonomy Extension Calculation Linkbase Document.				
101.DEF**	Inline XBRL Taxonomy Extension Definition Linkbase Document.				
101.LAB**	Inline XBRL Taxonomy Extension Label Linkbase Document.				
101.PRE**	Inline XBRL Taxonomy Extension Presentation Linkbase Document.				
104	The cover page from the Company's Annual Report on Form 10-K for the year ended December 31, 2020, has been formatted in Inline XBRL.				

^ Filed herewith

* The certifications attached as Exhibit 32.1 and 32.2 that accompany this Annual Report on Form 10-K are not deemed filed with the Securities and Exchange Commission and are not to be incorporated by reference into any filing of Calithera Biosciences, Inc. under the Securities Act of 1933, as amended, or the Securities Exchange Act of 1934, as amended, whether made before or after the date of this Annual Report on Form 10-K, irrespective of any general incorporation language contained in such filing.

** Attached as Exhibit 101 to this Annual Report on Form 10-K formatted in XBRL (Extensible Business Reporting Language): (i) Consolidated Balance Sheets, (ii) Consolidated Statements of Operations, (iii) Consolidated Statements of Comprehensive Loss, (iv) Consolidated Statements of Cash Flows, (v) Consolidated Statements of Stockholders' Equity; and (vi) Notes to Consolidated Financial Statements, tagged as blocks of text and including detailed tags.

† Confidential treatment has been granted with respect to certain portions of this exhibit. Omitted portions have been filed separately with the Securities and Exchange Commission.

SIGNATURES

Pursuant to the requirements of Section 13 or 15(d) of the Securities Exchange Act of 1934, as amended, the Registrant has duly caused this Report to be signed on its behalf by the undersigned, thereunto duly authorized**.**

Calithera Biosciences, Inc.

Date: March 16, 2021

By: /s/ Susan M. Molineaux

Susan M. Molineaux, Ph.D.
President and Chief Executive Officer

POWER OF ATTORNEY

Each person whose individual signature appears below hereby authorizes and appoints Susan M. Molineaux and Stephanie Wong, and each of them, with full power of substitution and resubstitution and full power to act without the other, as his or her true and lawful attorney-in-fact and agent to act in his or her name, place and stead and to execute in the name and on behalf of each person, individually and in each capacity stated below, and to file any and all amendments to this Annual Report on Form 10-K and to file the same, with all exhibits thereto, and other documents in connection therewith, with the Securities and Exchange Commission, granting unto said attorneys-in-fact and agents, and each of them, full power and authority to do and perform each and every act and thing, ratifying and confirming all that said attorneys-in-fact and agents or any of them or their or his or her substitute or substitutes may lawfully do or cause to be done by virtue thereof.

Pursuant to the requirements of the Securities Exchange Act of 1934, as amended, this Report has been signed below by the following persons on behalf of the Registrant in the capacities and on the dates indicated.

Name	Title	Date
/s/ Susan M. Molineaux **Susan M. Molineaux, Ph.D.**	President, Chief Executive Officer and Director *(Principal Executive Officer)*	March 16, 2021
/s/ Stephanie Wong **Stephanie Wong**	Chief Financial Officer and Secretary *(Principal Financial and Accounting Officer)*	March 16, 2021
/s/ Sunil Agarwal **Sunil Agarwal, M.D.**	Director	March 16, 2021
/s/ Jonathan G. Drachman **Jonathan G. Drachman, M.D.**	Director	March 16, 2021
/s/ Scott Garland **Scott Garland**	Director	March 16, 2021
/s/ Jean M. George **Jean M. George**	Director	March 16, 2021
/s/ Suzy Jones **Suzy Jones**	Director	March 16, 2021
/s/ Deepa R. Pakianathan **Deepa R. Pakianathan, Ph.D.**	Director	March 16, 2021
/s/ Blake Wise **Blake Wise**	Director	March 16, 2021
/s/ H. Ward Wolff **H. Ward Wolff**	Director	March 16, 2021

Management Team

Susan M. Molineaux, Ph.D.
Founder President and Chief Executive Officer
Keith Orford, MD, Ph.D.
Chief Medical Officer
Stephanie Wong
Chief Financial Officer and Secretary
Christopher J. Molineaux, Ph.D.
Senior Vice President of Development
Frank Parlati, Ph.D.
Senior Vice President of Research
Sumita Ray
Senior Vice President, General Counsel and Chief Compliance Officer
Eric B. Sjogren, Ph.D.
Senior Vice President of Drug Discovery
Susan Demo, Ph.D.
Vice President of R&D Operations

Board of Directors

Sunil Agarwal, M.D.
Chief Development Officer and Head Portfolio Strategy
Sana Biotechnology
Jonathan Drachman, M.D.
Chief Executive Officer
Neoleukin Therapeutics
Scott Garland
Chief Executive Officer
PACT Pharma
Jean M. George
General Partner
Advanced Technology Ventures
Suzy Jones
Founder and Managing Partner
DNA Ink
Susan M. Molineaux, Ph.D.
Founder, President and Chief Executive Officer
Deepa R. Pakianathan, Ph.D.
Managing Member
Delphi Ventures
Blake Wise
Chief Executive Officer
Novome Biotechnologies
H. Ward Wolff
Former Chief Financial Officer and EVP
Sangamo Therapeutics

Stockholder Information

Corporate Headquarters
Calithera Biosciences, Inc.
343 Oyster Point Boulevard, Suite 200
South San Francisco, CA 94080
Stockholder Inquiry
Requests for information may be sent to Investor Relations at our Corporate Headquarters or by visiting the investor relations portion of our website at:
www.calithera.com
Stock Listing
NASDAQ: CALA
Transfer Agent
American Stock Transfer & Trust Company, LLC
6201 15th Avenue Brooklyn, New York 11219
Legal Counsel
Cooley LLP
Palo Alto, California
Independent Registered Public Accounting Firm
Ernst & Young LLP
Redwood City, California

Calithera Biosciences, Inc.
343 Oyster Point Boulevard, Suite 200
South San Francisco, CA 94080

www.calithera.com