Filed Pursuant to Rule 424(b)(5)
Registration No. 333-219791

PROSPECTUS SUPPLEMENT
(TO PROSPECTUS DATED AUGUST 18, 2017)

$50,000,000

Common Stock

We have entered into a certain Open Market Sale Agreement, or sales agreement, with Jefferies LLC, or Jefferies, relating to shares of our common stock, par value $0.0001 per share, offered by this prospectus supplement and the accompanying prospectus. In accordance with the terms of the sales agreement, we may offer and sell shares of our common stock having an aggregate offering price of up to $50,000,000 from time to time through Jefferies, acting as our agent.

Our common stock is listed on the Nasdaq Global Select Market under the symbol "CALA." On December 5, 2019, the last reported sale price of our common stock on the Nasdaq Global Select Market was $4.42 per share.

Sales of our common stock, if any, under this prospectus supplement and the accompanying prospectus will be made in sales deemed to be "at the market offerings" as defined in Rule 415 promulgated under the Securities Act of 1933, as amended, or the Securities Act. Jefferies is not required to sell any specific amount of securities, but will act as our sales agent using commercially reasonable efforts consistent with its normal trading and sales practices, on mutually agreed terms between Jefferies and us. There is no arrangement for funds to be received in any escrow, trust or similar arrangement.

The compensation to Jefferies for sales of common stock sold pursuant to the sales agreement will be an amount up to 3% of the gross proceeds of any shares of common stock sold under the sales agreement. In connection with the sale of the common stock on our behalf, Jefferies will be deemed to be an "underwriter" within the meaning of the Securities Act and the compensation of Jefferies will be deemed to be underwriting commissions or discounts. We have also agreed to provide indemnification and contribution to Jefferies with respect to certain liabilities, including liabilities under the Securities Act or the Exchange Act of 1934, as amended.

Our business and an investment in our common stock involve significant risks. These risks are described under the caption "Risk Factors" beginning on page S-11 of this prospectus supplement and on page 8 of the accompanying prospectus and in the documents incorporated by reference into this prospectus supplement.

Neither the Securities and Exchange Commission nor any state securities commission has approved or disapproved of these securities or passed upon the accuracy or adequacy of this prospectus or the accompanying prospectus. Any representation to the contrary is a criminal offense.

Jefferies

December 6, 2019

TABLE OF CONTENTS

PROSPECTUS SUPPLEMENT

PROSPECTUS

ABOUT THIS PROSPECTUS SUPPLEMENT

This prospectus supplement is part of a registration statement that we have filed with the Securities and Exchange Commission, or the SEC, utilizing a “shelf” registration process. Under the shelf registration process, we may offer shares of our common stock having an aggregate offering price of up to $250,000,000. Under this prospectus supplement, we may offer shares of our common stock having an aggregate offering price of up to $50,000,000 from time to time at prices and on terms to be determined by market conditions at the time of offering.

We have terminated the sales agreement dated as of August 7, 2017 with Cowen and Company, LLC, which we refer to as the Cowen Agreement, and no additional offers will be made under the prospectus supplement relating to the Cowen Agreement filed with the Securities and Exchange Commission on August 18, 2017.

Before buying any of the common stock that we are offering, we urge you to carefully read this prospectus supplement and the accompanying prospectus and all of the information incorporated by reference herein and therein, as well as the additional information described under the sections titled “Where You Can Find More Information” and “Incorporation of Documents by Reference.” These documents contain important information that you should consider when making your investment decision.

We provide information to you about this offering of shares of our common stock in this prospectus supplement and the accompanying prospectus, which describes the specific details regarding this offering. If information in this prospectus supplement is inconsistent with the accompanying prospectus or documents incorporated by reference in this prospectus supplement filed prior to the date of this prospectus supplement, you should rely on this prospectus supplement. However, if any statement in one of these documents is inconsistent with a statement in another document having a later date—for example, a document incorporated by reference in this prospectus supplement—the statement in the document having the later date modifies or supersedes the earlier statement as our business, financial condition, results of operations and prospects may have changed since the earlier dates.

You should rely only on the information contained in this prospectus supplement and the accompanying prospectus or in any free writing prospectus prepared by us or on our behalf. We have not, and Jefferies has not, authorized any other person to provide you with different information. If anyone provides you with different or inconsistent information, you should not rely on it. We are not, and Jefferies is not, making an offer to sell these securities in any jurisdiction where the offer or sale is not permitted. You should assume that the information appearing in this prospectus supplement is accurate only as of the date on the front cover of this prospectus supplement. Our business, financial condition, results of operations and prospects may have changed since that date.

Information contained on our website is not part of this prospectus supplement and the accompanying prospectus. We are offering to sell, and seeking offers to buy, shares of common stock only in jurisdictions where offers and sales are permitted. The distribution of this prospectus supplement and the offering of the common stock in certain jurisdictions may be restricted by law. Persons outside the United States who come into possession of this prospectus supplement must inform themselves about, and observe any restrictions relating to, the offering of the common stock and the distribution of this prospectus supplement outside the United States. This prospectus supplement and the accompanying prospectus do not constitute, and may not be used in connection with, an offer to sell, or a solicitation of an offer to buy, any securities offered by this prospectus supplement or the accompanying prospectus by any person in any jurisdiction in which it is unlawful for such person to make such an offer or solicitation.

INDUSTRY AND MARKET DATA

We obtained the industry and market data in this prospectus supplement and the documents incorporated by reference herein from our own research as well as from industry and general publications, surveys and studies conducted by third parties. These data involve a number of assumptions and limitations, and you are cautioned not to give undue weight to such estimates. In addition, projections, assumptions and estimates of our future performance and the future performance of the industry in which we operate is necessarily subject to a high degree of uncertainty and risk due to a variety of factors, including those described in the section titled “Risk Factors” and elsewhere in this prospectus supplement and the accompanying prospectus. These and other factors could cause results to differ materially from those expressed in the estimates made by the independent parties and by us.

PROSPECTUS SUPPLEMENT SUMMARY

This summary highlights selected information contained elsewhere in this prospectus supplement and the accompanying prospectus or incorporated by reference in this prospectus supplement and the accompanying prospectus, and does not contain all of the information that you need to consider in making your investment decision. You should carefully read the entire prospectus supplement, the accompanying prospectus and any related free writing prospectus, including the risks of investing in our securities discussed under the section titled "Risk Factors" contained in this prospectus supplement and the accompanying prospectus and any related free writing prospectus, and under similar headings in the other documents that are incorporated by reference into this prospectus supplement and the accompanying prospectus. You should also carefully read the information incorporated by reference into this prospectus supplement and the accompanying prospectus, including our financial statements, and the exhibits to the registration statement of which this prospectus supplement is a part.

Calithera Biosciences, Inc.

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 may opportunistically develop therapeutics outside of oncology where we can leverage our existing expertise in immune cell metabolism to treat life-threatening diseases with unmet need.

Currently we have multiple product candidates in our development pipeline. Our product candidate telaglenastat is an oral inhibitor of glutaminase, a critical enzyme in tumor cells that controls utilization of the nutrient glutamine. Telaglenastat is designed to take 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 has demonstrated synergistic antitumor effects with multiple anticancer therapies in preclinical studies. The telaglenastat development program includes two Phase 2 randomized double blind, placebo-controlled clinical trials of telaglenastat for the treatment of renal cell carcinoma, or RCC. We recently reported the results of the randomized, double blind, placebo-controlled ENTRATA study of telaglenastat, which met its primary endpoint. ENTRATA provides the first clinical proof of concept for telaglenastat in a randomized trial. Telaglenastat is also being evaluated in a large randomized double blind, placebo-controlled trial called CANTATA in 445 patients with RCC. Top-line results are expected from this potential registration trial in the second half of 2020. Our product candidate, INCB001158, also known as CB-1158, is an oral inhibitor of arginase, an enzyme that depletes the amino acid arginine, a key metabolic nutrient for T-cells. INCB001158 is being co-developed with 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. Arginase inhibitors also have potential in the treatment of cystic fibrosis; accordingly, we have selected CB-280, a unique oral arginase inhibitor, for the treatment of cystic fibrosis patients. We have completed a Phase 1 trial to evaluate the

safety, tolerability and pharmacokinetic profile of oral CB-280 in healthy volunteers and plan to open a study in Cystic Fibrosis, or CF, patients in the first half of 2020. We have two earlier stage immunotherapy programs which include our candidate CB-708, which targets CD73, an enzyme in the tumor microenvironment that produces adenosine, as well an IL4I1 inhibitor program.

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. Telaglenastat, when given alone or in combination with a variety of other anti-cancer agents, affects multiple pathways in tumor cells, leading to energetic blocks, inhibition of DNA synthesis, oxidative stress, and cell cycle disruptions. Because telaglenastat has multiple mechanisms for impacting cellular metabolism, it has anti-tumor effects on a number of different tumor types in combination with a variety of different agents, including tyrosine kinase inhibitors, mTOR inhibitors, taxanes, 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 are currently developing telaglenastat in combination with standard therapies in a select set of solid tumors. Our primary focus is in RCC where we are currently evaluating telaglenastat in a large randomized Phase 2 potential registration trial and multiple non-randomized combination trials. Because of the recent progress in developing new therapies for the treatment of patients today, the RCC market, according to market research, is expected to grow significantly, from over $2 billion to $7 billion in 2025.

Telaglenastat Evaluation in Renal Cell Carcinoma

The telaglenastat development program includes two Phase 2 randomized double blind, placebo-controlled clinical trials of telaglenastat for the treatment of RCC. Telaglenastat is being investigated in the CANTATA trial (NCT03428217), which is designed with registrational intent. It is a global, randomized, double-blind trial of 445 patients, 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, including at least one vascular endothelial growth factor tyrosine kinase inhibitor or the combination of nivolumab and ipilimumab. The primary endpoint is PFS by blinded independent review, and a key secondary endpoint is overall survival. Patients will be stratified by International Metastatic Renal Cell Carcinoma Database Consortium, or IMDC, risk category and prior treatment with anti-PD(L)1 therapy. The study has 85% power to show a 31% improvement in progression free survival. In support of the CANTATA trial, Exelixis, Inc. has entered into a material supply agreement with us for cabozantinib. The U.S. Food and Drug Administration, or FDA, has granted Fast Track designation to telaglenastat in combination with cabozantinib, for the treatment of patients with metastatic RCC who have received one or two prior lines of therapy We completed enrollment of the CANTATA trial in October and release of top-line results is expected in the second half of 2020.

The ENTRATA trial (NCT03163667) is 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 (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 progression-free survival, or 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%. The secondary endpoint of overall survival is not yet mature.

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 $\geq$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 Pfizer's talazoparib and palbociclib

In March 2019, we initiated a Phase 1/2 clinical trial of telaglenastat in combination with Pfizer's poly adenosine disphosphate ribose polymerase (PARP) inhibitor, talazoparib, in patients with solid tumors. In July 2019, we initiated a trial of the combination of telaglenastat plus the CDK 4/6 inhibitor, palbociclib, in patients with KRAS mutated colorectal cancer, or CRC, and KRAS mutated non-small cell lung carcinoma, or NSCLC. The trials in combination with palbociclib and talazoparib are part of a clinical collaboration with Pfizer, announced in October 2018, in which Pfizer will provide palbociclib and talazoparib, as well as financial support.

Evaluation of Telaglenastat in Combination with the Immunotherapy Agent Nivolumab

In August 2016, we initiated a Phase 1/2 clinical trial of telaglenastat in combination with the PD-1 inhibitor nivolumab in patients with RCC, melanoma, and NSCLC. The Phase 1/2 study is designed to assess the safety, pharmacokinetics and pharmacodynamics of telaglenastat and nivolumab. A collaboration with Bristol-Myers Squibb, originally announced in December 2016 to evaluate nivolumab in combination with telaglenastat in patients with RCC, was expanded in May 2017 to include melanoma and NSCLC. In November 2017, the melanoma cohort was expanded to enroll additional patients and the collaboration was expanded such that subsequent melanoma development costs would be shared, and a joint development committee was established to guide the development and regulatory strategy of the combination therapy. In July 2019, with the enrollment of the trial complete, the collaboration with Bristol-Myers Squibb was discontinued. The totality of the data has informed us towards future development and an additional trial of telaglenastat in combination with a PD-1 inhibitor is being designed.

The NRF2/KEAP1 pathway is known to drive the development of certain cancer, including a significant proportion of NSCLC and HNSCC, through the regulation of reactive oxygen species (ROS) in a manner that requires glutaminase activity. 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 exquisitely sensitive to the inhibition of glutaminase activity by telaglenastat (CB-839). Finally, recently presented clinical data demonstrate that that activation of this pathway, either through the loss of KEAP1 function or activation of NRF2, results in very poor outcomes in NSCLC patients receiving front line standard of care chemotherapy or chemoimmunotherapy. The clear mechanistic rationale, strong preclinical data, and high unmet medical need in the NSCLC population have motivated a clinical study that will evaluate telaglenastat, in combination with SOC chemoimmunotherapy in front line NSCLC patients with tumors that harbor mutations in either KEAP1 or NRF2 that activate this pathway. This trial is expected to begin in the first half of 2020.

Evaluation of Telaglenastat in PIK3CA-mutated Colorectal Carcinoma (CRC)

CRC is one of the most common cancers with approximately 140,250 new cases and 50,630 deaths in the U.S. in 2018, according to the American Cancer Society. The oncogene PIK3CA, which encodes the p110α catalytic subunit of phosphatidylinositol-3-kinase α, is one of the most frequently mutated oncogenes in human cancers; mutations in PIK3CA are found in approximately 10%-20% of CRC, which resulted in between 14,000 and 28,000 new cases of mutated PIK3CA CRC in the United States in 2018.

An academic research group at Case Western Reserve University demonstrated that single agent telaglenastat inhibits the growth of CRC tumors with PIK3CA mutations in immune-compromised mice, but the growth of CRC tumors with a normal PIK3CA gene were not inhibited. Remarkably, the combination of telaglenastat with 5-florouracil induced complete and long-lasting tumor regressions in animals bearing PIK3CA mutant CRC tumors, but not tumors with normal PIK3CA, suggesting that this combination therapy may be a unique and effective approach in the clinic.

An investigator-sponsored clinical trial was initiated by Drs. Jennifer Eads, Alok Khorana, and Neal Meropol, at the Case Western Comprehensive Cancer Center. This research is supported by a Stand Up To Cancer Colorectal Cancer Dream Team Translational Research Grant (Grant Number: SU2C-AACR-DT22-17). The Phase 1 portion of the trial is designed to determine safety and the recommended dose of the combination of telaglenastat and capecitabine in patients with advanced treatment-refractory solid tumors, while the Phase 2 portion of the trial is designed to evaluate activity of the regimen in patients with late line PIK3CA mutant colorectal cancer. 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. The recommended Phase 2 dose for the combination is telaglenastat at 800 mg BID with capecitabine at 1000 mg/m^2 BID. 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 Development Opportunities

Telaglenastat is the subject of a number of additional investigator-sponsored clinical trials. Phase 2 trials are ongoing and recruiting patients with RAS wild-type CRC and myelodysplastic syndrome (MDS). Interim MDS data will be presented at the American Society of Hematology meeting in

December 2019. An additional investigator trial of telaglenastat in combination with niraparib for the treatment of patients with platinum resistant BRCA-wild type ovarian cancer patients is also open for enrollment.

Telaglenastat is also available under NIH/NCI Cancer Therapy Evaluation Program (CTEP) collaborative agreement for clinical and non-clinical studies. A Phase 1/2 trial sponsored by CTEP of telaglenastat in combination with osimertinib for the treatment of patients with EGFR-mutated Stage IV non-small cell lung cancer, and a Phase I trial of telaglenastat for the treatment of patients with IDH mutant astrocytoma have recently opened. In addition a CTEP trial of telaglenastat in combination with carfilzomib and dexamethasone for the treatment of multiple myeloma is ongoing. CTEP plans to initiate an additional trial of telaglenastat for the treatment of soft tissue sarcoma; the study design is currently being finalized.

INCB001158

Our product candidate INCB001158, which is a potent and selective orally bioavailable inhibitor of the enzyme arginase, was discovered by us and is being co-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. We presented monotherapy data in June 2017 at the American Society of Clinical Oncology, or ASCO, annual meeting. In September 2019, data were presented at the European Society for Medical Oncology (ESMO) of INCB001158 as a monotherapy and in combination with the checkpoint inhibitor pembrolizumab in microsatellite stable (MSS) colorectal carcinoma patients. The study was designed as a dose escalation of INCB001158 alone and in combination with pembrolizumab followed by expansion cohorts which followed a Simon 2 Stage design. There were three monotherapy expansion cohorts (non-small cell lung cancer, colorectal carcinoma and other solid tumors) and eight combination expansion cohorts, including PD-(L)1-naïve (MSS colorectal carcinoma, head and neck cancer, gastric cancer, mesothelioma) and PD-(L)1 refractory (non-small cell lung cancer, urothelial carcinoma, melanoma, and MSI colorectal carcinoma) patients. Results were as of the data cut-off of July 22, 2019.

Efficacy results for the pembrolizumab combination were presented for the PD-(L)1-naïve MSS colorectal carcinoma (CRC) patient cohort, which has advanced to stage 2 of a Simon 2-stage design. Among 43 response-evaluable patients who had received a median of 3 prior therapies, 3 patients achieved a confirmed partial response (7%); the historical overall response rate is 0-1% in third-line (and beyond) MSS CRC patients treated with checkpoint inhibitor therapies. Two of the three responders are ongoing at the time of data cutoff with a duration of response of 2.4+ and 7+ months respectively. The third responder had a duration of response of 6.7 months. The six month PFS rate for the cohort was 20%. Pharmacodynamic increases in total intratumoral CD8+ cells were seen post-treatment with INCB001158 + pembrolizumab in MSS CRC patients.

The colorectal carcinoma monotherapy cohort has advanced to stage 2 of a Simon 2-stage design. Among 33 response-evaluable MSS CRC patients, one patient achieved a confirmed partial response (3%) and one patient achieved stable disease lasting seven months. Both patients had disease progression within six months on their immediately preceding line of therapy. The disease control rate for the monotherapy MSS CRC cohort was 27%. INCB001158 inhibited plasma arginase activity at all doses and induced dose-related increases in plasma arginine, including a mean three-fold increase at the recommended phase 2 dose of 100 mg bid.

The HNSCC cohort of PD-1 naïve patients receiving pembrolizumab and INCB001158 has also advanced to stage 2 of a Simon 2-stage design and enrollment in stage 2 is currently ongoing.

A total of 85 patients with advanced solid tumors were treated with INCB001158 as a monotherapy in doses of 50 to 150mg bid and were evaluable for safety. A maximum tolerated dose was not reached. Immune-related adverse events included one dose-limiting toxicity (DLT) each of Grade 2 malaise (at 150mg) and Grade 3 colitis (100mg). Clinically significant urea cycle inhibition was not seen. A total of 114 PD-(L)1-naïve and PD-(L)1 refractory patients were treated in INCB001158 in combination with pembrolizumab and evaluable for safety across multiple disease specific cohorts. The overall frequency and severity of immune related adverse events was consistent with the pembrolizumab safety profile.

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. The parties are collaborating on and co-funding the development of the licensed products, with Incyte bearing 70% and us bearing 30% of global development costs. The parties will share profits and losses in the U.S., with 60% to Incyte and 40% to us. We will have the right to co-detail the licensed products in the U.S., and Incyte will pay us tiered royalties ranging from the low to mid-teens on net sales of licensed products outside the U.S. We may opt out of our co-funding obligation, in which case the U.S. profit sharing will no longer be in effect, and Incyte will pay us tiered royalties ranging from the low to mid-double digits on net sales of licensed products both in the U.S. and outside the U.S., and additional royalties to reimburse us for previously incurred development costs.

Our Arginase Inhibitor CB-280

Arginase has been proposed to be critical in the pathophysiology of several non-oncology diseases, including cystic fibrosis (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. Arginase plays an important role in the pathophysiology of CF airway disease. 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 immune response and impaired airway function. It is known that airways of patients with CF have lower than normal nitric oxide (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.

We, along with our pre-clinical collaborators, have validated arginase inhibitors in mouse models of CF. 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 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 is expected to start enrollment in early 2020, which will test multiple doses of CB-280 compared to placebo in 32 adult CF patients to determine a safe dose range for CB-280 in CF patients. 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 in order to improve lung function. For the entire study, patients will continue their existing therapies for CF (including CFTR modulators). 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. 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.

Our CD73 Inhibitor CB-708

CD73 is an enzyme in the tumor microenvironment 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. We anticipate that our CD73 inhibitor will enter clinical trials in 2020.

Our IL4I1 Inhibitor Program

IL4I1 is an enzyme that is primarily expressed by tumor cells and antigen presenting cells, and produces hydrogen peroxide, an inhibitor of T-cell function. IL4I1 expression has been correlated with poor outcomes in several tumor types, has a potential role in immune invasion and may decrease the ability of checkpoint therapy to stimulate an anti-tumor immune response. IL4I1 expression is elevated in multiple tumor types with particularly high expression in ovarian and B-cell tumors. We have developed an investigational first-in-class, potent, orally available IL4I1 inhibitor. Preclinical data were presented at the SITC meeting in November and demonstrated that our novel small-molecule inhibitor of IL4I1 has single-agent anti-tumor activity in syngeneic mouse tumor models and augments the activity of checkpoint inhibitors.

Risks Associated with our Business

Our business is subject to numerous risks and uncertainties, including those highlighted in the section titled “Risk Factors” immediately following this prospectus supplement 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 had an accumulated deficit of $264.4 million as of September 30, 2019.
- We will need substantial additional funding and may be unable to raise capital when needed, which would force us to delay, reduce or eliminate our product development programs or commercialization efforts.
- Our approach to discovery and development of product candidates that target tumor metabolism and tumor immunology is unproven and may never lead to marketable products.
- We are very early in our development efforts, which may not be successful.
- 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.
- 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.
- 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.
- Our arginase inhibitors program in hematology and oncology indications, including CB-1158, is reliant in part on Incyte for the successful development and commercialization in a timely manner. If Incyte does not devote sufficient resources to CB-1158’s development, is unsuccessful in its efforts, or chooses to terminate its agreement with us, our business, operating results and financial condition will be harmed.
- If we are alleged to infringe intellectual property rights of third parties, our business could be harmed.

- 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.
- We face substantial competition from major pharmaceutical companies, specialty pharmaceutical companies and biotechnology companies worldwide.

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.

In addition, we are an "emerging growth company" as defined in the Jumpstart Our Business Startups Act, or the JOBS Act, enacted in April 2012, and therefore we take advantage of certain exemptions from various public company reporting requirements, including not being required to have our internal control over financial reporting audited by our independent registered public accounting firm pursuant to Section 404(b) of the Sarbanes-Oxley Act of 2002, reduced disclosure obligations regarding executive compensation in our periodic reports and proxy statement and exemptions from the requirements of holding a nonbinding advisory vote on executive compensation and any golden parachute payments not previously approved. We may take advantage of these exemptions until the earlier of the fifth anniversary of the closing of our initial public offering in October 2014 or until we are no longer an "emerging growth company."

Corporate Information

We were incorporated in Delaware in March 2010 as Protein Activation Therapeutics, Inc. and subsequently changed our name to Calithera Biosciences, Inc. Our headquarters are located at 343 Oyster Point Blvd., Suite 200, South San Francisco, California 94080, and our telephone number is (650) 870-1000. Our website address is www.calithera.com. The information contained on, or that can be accessed through, our website is not part of, and is not incorporated by reference into this prospectus supplement and the accompanying prospectus and should not be considered to be part of this prospectus supplement and the accompanying prospectus. Investors should not rely on any such information in deciding whether to purchase our common stock.

"Calithera," the Calithera logo and other trademarks or service marks of Calithera Biosciences, Inc. appearing in this prospectus supplement and the accompanying prospectus are the property of Calithera Biosciences, Inc. Other trademarks, service marks or trade names appearing in this prospectus supplement and the accompanying prospectus are the property of their respective owners. We do not intend our use or display of other companies' trade names, trademarks or service marks to imply a relationship with, or endorsement or sponsorship of us by, these other companies.

The Offering

Common stock offered by us	Shares of our common stock, par value $0.0001 per share, with an aggregate sale price of up to $50,000,000.
Common stock to be outstanding after this offering	Up to 65,087,521 shares, assuming the sale of 11,312,217 shares of our common stock in this offering at a public offering price of $4.42 per share, which was the last reported sale price of our common stock on the Nasdaq Global Select Market on December 5, 2019. The actual number of shares issued will vary depending on the sales price under this offering.
Manner of offering	"At-the-market" offering that may be made from time to time through or to Jefferies, as sales agent and/or principal. See "Plan of Distribution" on page 17.
Use of proceeds	We intend to use the net proceeds from this offering, if any, to fund our clinical trials and for working capital and general corporate purposes. See "Use of Proceeds" on page 15.
Risk factors	Investment in our securities involves a high degree of risk. You should read the "Risk Factors," beginning on page S-11 of this prospectus supplement and on page 8 of the accompanying prospectus and in the documents incorporated by reference into this prospectus supplement for a discussion of factors to consider before deciding to purchase shares of our common stock.
Nasdaq Global Select Market Symbol:	"CALA"

The number of our shares of common stock outstanding after this offering is based on 53,775,304 shares of common stock outstanding as of September 30, 2019, and excludes:

- 3,450,220 shares of common stock issuable upon the exercise of options outstanding at a weighted-average exercise price of $7.90 per share;
- 16,278 shares of common stock reserved for future issuance under our 2014 Equity Incentive Plan, as well as any automatic increases in the number of shares of common stock reserved for future issuance under this plan;
- 1,000,000 shares reserved for future issuance under our 2018 Inducement Plan; and
- 596,023 shares reserved for future issuance under our 2014 Employee Stock Purchase Plan, as well as any automatic increases in the number of shares of common stock reserved for future issuance under this plan.

RISK FACTORS

You should consider carefully the risks described below and discussed under the section titled "Risk Factors" contained in our Annual Report on Form 10-K for the year ended December 31, 2018, and in our subsequent Quarterly Reports on Form 10-Q as updated by our subsequent filings under the Securities Exchange Act of 1934, as amended, or the Exchange Act, each of which is incorporated by reference in this prospectus supplement and the accompanying prospectus in their entirety, together with other information in this prospectus supplement and the accompanying prospectus, and the information and documents incorporated by reference in this prospectus supplement and the accompanying prospectus, and any free writing prospectus that we have authorized for use in connection with this offering before you make a decision to invest in our common stock. If any of the following events actually occur, our business, financial condition, results of operations or cash flow could be harmed. This could cause the trading price of our common stock to decline and you may lose all or part of your investment. The risks below and incorporated by reference in this prospectus supplement and the accompanying prospectus are not the only ones we face. Additional risks not currently known to us or that we currently deem immaterial may also affect our business operations. Please also read carefully the section below titled "Special Note Regarding Forward-Looking Statements."

Additional Risks Relating To The Offering

Our management team may invest or spend the proceeds of this offering in ways with which you may not agree or in ways which may not yield a significant return.

Our management will have broad discretion over the use of proceeds from this offering. The net proceeds from this offering will be used for working capital and general corporate purposes, which may include, among other things, funding research and development, clinical trials, vendor payables, potential regulatory submissions, hiring additional personnel and capital expenditures. We may also use a portion of the net proceeds to in-license, acquire or invest in complementary businesses or products; however, we have no current commitments or obligations to do so.

Our management will have considerable discretion in the application of the net proceeds, and you will not have the opportunity, as part of your investment decision, to assess whether the proceeds are being used appropriately. The net proceeds may be used for corporate purposes that do not increase our operating results or enhance the value of our common stock.

You may experience future dilution as a result of future equity offerings.

To raise additional capital, we may in the future offer additional shares of our common stock or other securities convertible into or exchangeable for our common stock at prices that may not be the same as the price per share in this offering. We may sell shares or other securities in any other offering at a price per share that is less than the price per share paid by investors in this offering, and investors purchasing shares or other securities in the future could have rights superior to existing stockholders. The price per share at which we sell additional shares of our common stock, or securities convertible or exchangeable into common stock, in future transactions may be higher or lower than the price per share paid by investors in this offering.

It is not possible to predict the actual number of shares we will sell under the sales agreement, or the gross proceeds resulting from those sales.

Subject to certain limitations in the sales agreement and compliance with applicable law, we have the discretion to deliver instruction to Jefferies to sell shares of our common stock at any time

throughout the term of the sales agreement. The number of shares that are sold through Jefferies after our instruction will fluctuate based on a number of factors, including the market price of our common stock during the sales period, the limits we set with Jefferies in any instruction to sell shares, and the demand for our common stock during the sales period. Because the price per share of each share sold will fluctuate during this offering, it is not currently possible to predict the number of shares that will be sold or the gross proceeds to be raised in connection with those sales.

The common stock offered hereby will be sold in "at the market offerings", and investors who buy shares at different times will likely pay different prices.

Investors who purchase shares in this offering at different times will likely pay different prices, and so may experience different levels of dilution and different outcomes in their investment results. We will have discretion, subject to market demand, to vary the timing, prices, and numbers of shares sold in this offering. In addition, subject to the final determination by our board of directors, there is no minimum or maximum sales price for shares to be sold in this offering. Investors may experience a decline in the value of the shares they purchase in this offering as a result of sales made at prices lower than the prices they paid.

SPECIAL NOTE REGARDING FORWARD-LOOKING STATEMENTS

This prospectus supplement and the accompanying prospectus and the documents we have filed with the SEC that are incorporated by reference contain "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 Exchange Act. These statements relate to future events or to our future operating or financial performance and involve known and unknown risks, uncertainties and other factors which may cause our actual results, performance or achievements to be materially different from any future results, performances or achievements expressed or implied by the forward-looking statements. Forward-looking statements may include, but are not limited to, statements about:

- our ability to fund our working capital requirements;
- our ability to obtain and maintain regulatory approval of our product candidates;
- our ability to successfully commercialize our product candidates;
- the rate and degree of market acceptance of our products that are approved;
- our estimates of our expenses, ongoing losses, future revenue, capital requirements and our needs for or ability to obtain additional financing;
- our expectation that our existing capital resources and the net proceeds from this offering will be sufficient to enable us to complete our planned clinical trials;
- our expectations with respect to the Incyte Collaboration Agreement;
- our ability to obtain and maintain intellectual property protection for our product candidates;
- our ability to identify and develop new product candidates;
- our ability to retain and recruit key personnel;
- our use of proceeds from this offering;
- our financial performance; and
- developments and projections relating to our competitors or our industry.

These risks are not exhaustive. Other sections of this prospectus supplement and the accompanying prospectus may include additional factors that could harm our business and financial performance. Moreover, we operate in a very competitive and rapidly changing environment. New risk factors emerge from time to time, and it is not possible for our management to predict all risk factors nor can we assess the impact of all factors on our business or the extent to which any factor, or combination of factors, may cause actual results to differ materially from those contained in, or implied by, any forward-looking statements.

All statements other than statements of historical facts contained in this prospectus supplement and the accompanying prospectus, including statements regarding our future financial condition, business strategy and plans, and objectives of management for future operations, are forward-looking statements. In some cases, you can identify forward-looking statements by words such as "anticipate," "believe," "continue," "could," "design," "estimate," "expect," "intend," "may," "plan," "potentially," "predict," "should," "will" or the negative of these terms or other similar expressions. These statements reflect our current views with respect to future events and are based on assumptions and are subject to risks and uncertainties. Given these uncertainties, you should not place undue reliance on these forward-looking statements. We discuss in greater detail many of these risks under the section titled "Risk Factors" contained in this prospectus supplement and the accompanying prospectus, in any free writing prospectuses we may authorize for use in connection with a specific offering, and in our most

recent annual report on Form 10-K and in our most recent quarterly report on Form 10-Q, as well as any amendments thereto reflected in subsequent filings with the SEC, which are incorporated by reference into this prospectus supplement and the accompanying prospectus in their entirety. Also, these forward-looking statements represent our estimates and assumptions only as of the date of the document containing the applicable statement. Unless required by law, we undertake no obligation to update or revise any forward-looking statements to reflect new information or future events or developments. You should read this prospectus supplement, the accompanying prospectus together with the documents we have filed with the SEC that are incorporated by reference and any free writing prospectus that we may authorize for use in connection with this offering completely and with the understanding that our actual future results may be materially different from what we expect. We qualify all of the forward-looking statements in the foregoing documents by these cautionary statements.

In addition, statements that “we believe” and similar statements reflect our beliefs and opinions on the relevant subject. These statements are based upon information available to us as of the date of this prospectus supplement, and while we believe such information forms a reasonable basis for such statements, such information may be limited or incomplete, and our statements should not be read to indicate that we have conducted an exhaustive inquiry into, or review of, all potentially available relevant information. These statements are inherently uncertain and investors are cautioned not to unduly rely upon these statements.

USE OF PROCEEDS

The amount of proceeds from this offering will depend upon the number of shares of our common stock sold and the market price at which they are sold. There can be no assurance that we will be able to sell any shares under or fully utilize the sales agreement with Jefferies as a source of financing. We intend to use the net proceeds, if any, from this offering for working capital and general corporate purposes, which may include, among other things, funding research and development, clinical trials, vendor payables, potential regulatory submissions, hiring additional personnel and capital expenditures. We may also use a portion of the net proceeds to in-license, acquire or invest in complementary businesses or products; however, we have no current commitments or obligations to do so.

The amounts and timing of our actual expenditures will depend on numerous factors, including our development and commercialization efforts, as well as the amount of cash used in our operations. We therefore cannot estimate with certainty the amount of net proceeds to be used for the purposes described above. We may find it necessary or advisable to use the net proceeds for other purposes, and we will have broad discretion in the application of the net proceeds. Pending the uses described above, we plan to invest the net proceeds from this offering in short-term, investment-grade, interest-bearing securities.

DILUTION

If you invest in our common stock, your interest will be diluted to the extent of the difference between the public offering price per share and the as adjusted net tangible book value per share of our common stock after this offering.

Our net tangible book value as of September 30, 2019, was $120.7 million, or $2.24 per share. Net tangible book value is total tangible assets less our total liabilities divided by the number of outstanding shares of common stock.

After giving effect to the sale of $50,000,000 of shares common stock in this offering at an assumed public offering price of $4.42 per share, which was the closing price of our common stock as reported on the Nasdaq Global Select Market on December 5, 2019, and after deducting offering commissions and expenses payable by us, our net tangible book value as of September 30, 2019, would have been $167.4 million, or $2.57 per share of common stock. This represents an immediate increase in net tangible book value of $0.33 per share to our existing stockholders and an immediate dilution in net tangible book value of $1.85 per share to investors participating in this offering. The following table illustrates this dilution per share to investors participating in this offering:

Assumed public offering price per share		$ 4.42
Net tangible book value per share as of September 30, 2019	$ 2.24	
Increase in net tangible book value per share attributable to new investors in offering	$ 0.33	
As adjusted net tangible book value per share after this offering		2.57
Dilution per share to new investors		$ 1.85

The above illustration of dilution per share to investors participating in this offering assumes no exercise of outstanding options to purchase our common stock.

The above discussion and table are based on shares of our common stock issued and outstanding after this offering as of September 30, 2019, and excludes:

- 3,450,220 shares issuable upon the exercise of options outstanding at a weighted-average exercise price of $7.90 per share;
- 16,278 shares of common stock reserved for future issuance under our 2014 Equity Incentive Plan, as well as automatic increases in the number of shares of common stock reserved for future issuances under this plan;
- 1,000,000 shares reserved for future issuance under our 2018 Inducement Plan; and
- 596,023 shares of common stock reserved for future issuance under our 2014 Employee Stock Purchase Plan, as well as automatic increases in the number of shares of common stock reserved for future issuances under this plan.

To the extent that any of these outstanding options are exercised, there will be further dilution to new investors.

PLAN OF DISTRIBUTION

We have entered into a sales agreement with Jefferies, under which we may offer and sell up to $50,000,000 of our shares of common stock from time to time through Jefferies acting as agent. Sales of our shares of common stock, if any, under this prospectus supplement and the accompanying prospectus will be made by any method that is deemed to be an “at the market offering” as defined in Rule 415(a)(4) under the Securities Act.

Each time we wish to issue and sell our shares of common stock under the sales agreement, we will notify Jefferies of the number of shares to be issued, the dates on which such sales are anticipated to be made, any limitation on the number of shares to be sold in any one day and any minimum price below which sales may not be made. Once we have so instructed Jefferies, unless Jefferies declines to accept the terms of such notice, Jefferies has agreed to use its commercially reasonable efforts consistent with its normal trading and sales practices to sell such shares up to the amount specified on such terms. The obligations of Jefferies under the sales agreement to sell our shares of common stock are subject to a number of conditions that we must meet.

The settlement of sales of shares between us and Jefferies is generally anticipated to occur on the second trading day following the date on which the sale was made. Sales of our shares of common stock as contemplated in this prospectus supplement will be settled through the facilities of The Depository Trust Company or by such other means as we and Jefferies may agree upon. There is no arrangement for funds to be received in an escrow, trust or similar arrangement.

We will pay Jefferies a commission up to 3% of the aggregate gross proceeds we receive from each sale of our shares of common stock. Because there is no minimum offering amount required as a condition to close this offering, the actual total public offering amount, commissions and proceeds to us, if any, are not determinable at this time. In addition, we have agreed to reimburse Jefferies for the fees and disbursements of its counsel, payable upon execution of the sales agreement, in an amount not to exceed $50,000, in addition to certain ongoing disbursements of its legal counsel. We estimate that the total expenses for the offering, excluding any commissions or expense reimbursement payable to Jefferies under the terms of the sales agreement, will be approximately $300,000. The remaining sale proceeds, after deducting any other transaction fees, will equal our net proceeds from the sale of such shares.

Jefferies will provide written confirmation to us before the open on The Nasdaq Global Select Market on the day following each day on which our shares of common stock are sold under the sales agreement. Each confirmation will include the number of shares sold on that day, the aggregate gross proceeds of such sales and the proceeds to us.

In connection with the sale of our shares of common stock on our behalf, Jefferies will be deemed to be an “underwriter” within the meaning of the Securities Act, and the compensation of Jefferies will be deemed to be underwriting commissions or discounts. We have agreed to indemnify Jefferies against certain civil liabilities, including liabilities under the Securities Act. We have also agreed to contribute to payments Jefferies may be required to make in respect of such liabilities.

The offering of our shares of common stock pursuant to the sales agreement will terminate upon the earlier of (i) the sale of all shares of common stock subject to the sales agreement and (ii) the termination of the sales agreement as permitted therein. We and Jefferies may each terminate the sales agreement at any time upon ten days’ prior notice.

This summary of the material provisions of the sales agreement does not purport to be a complete statement of its terms and conditions. A copy of the sales agreement is filed as an exhibit to a current report on Form 8-K filed under the Exchange Act and incorporated by reference in this prospectus supplement.

Jefferies and its affiliates may in the future provide various investment banking, commercial banking, financial advisory and other financial services for us and our affiliates, for which services they may in the future receive customary fees. In the course of its business, Jefferies may actively trade our securities for its own account or for the accounts of customers, and, accordingly, Jefferies may at any time hold long or short positions in such securities.

A prospectus supplement and the accompanying prospectus in electronic format may be made available on a website maintained by Jefferies, and Jefferies may distribute the prospectus supplement and the accompanying prospectus electronically.

LEGAL MATTERS

Cooley LLP, Palo Alto, California, will pass upon the validity of the shares of common stock offered hereby. As of the date of this prospectus supplement, certain Cooley LLP attorneys and GC&H Investments, LLC and GC&H Investments, entities comprised of partners and associates of Cooley LLP, beneficially own an aggregate of 2,621 shares of our common stock. Jefferies LLC is being represented by Goodwin Procter LLP, Redwood City, California in connection with this offering.

EXPERTS

Ernst & Young LLP, independent registered public accounting firm, has audited our consolidated financial statements included in our Annual Report on Form 10-K for the year ended December 31, 2018, as set forth in their report, which is incorporated by reference in this prospectus supplement and the accompanying prospectus and elsewhere in the registration statement. Our financial statements are incorporated by reference in reliance on Ernst & Young LLP's report, given on their authority as experts in accounting and auditing.

WHERE YOU CAN FIND ADDITIONAL INFORMATION

This prospectus supplement is part of the registration statement on Form S-3 we filed with the SEC under the Securities Act and does not contain all the information set forth in the registration statement. Whenever a reference is made in this prospectus supplement to any of our contracts, agreements or other documents, the reference may not be complete and you should refer to the exhibits that are a part of the registration statement or the exhibits to the reports or other documents incorporated by reference into this prospectus for a copy of such contract, agreement or other document. Because we are subject to the information and reporting requirements of the Exchange Act, we file annual, quarterly and current reports, proxy statements and other information with the SEC. Our SEC filings are available to the public over the Internet at the SEC's website at http://www.sec.gov.

INCORPORATION OF CERTAIN INFORMATION BY REFERENCE

The SEC allows us to "incorporate by reference" information from other documents that we file with it, which means that we can disclose important information to you by referring you to those documents. The information incorporated by reference is considered to be part of this prospectus supplement and the accompanying prospectus. Information in this prospectus supplement supersedes information incorporated by reference that we filed with the SEC prior to the date of this prospectus supplement, while information that we file later with the SEC will automatically update and supersede the information in this prospectus supplement. We incorporate by reference into this prospectus supplement and the registration statement of which this prospectus is a part the information or documents listed below that we have filed with the SEC (Commission File No. 001-36644):

- our Annual Report on Form 10-K for the year ended December 31, 2018, filed with the SEC on March 7, 2019;
- our Quarterly Report on Form 10-Q for the quarter ended March 31, 2019, filed with the SEC on May 9, 2019;
- our Quarterly Report on Form 10-Q for the quarter ended June 30, 2019, filed with the SEC on August 8, 2019;
- our Quarterly Report on Form 10-Q for the quarter ended September 30, 2019, filed with the SEC on November 12, 2019;
- the information specifically incorporated by reference in our Annual Report on Form 10-K for the year ended December 31, 2018, from our definitive proxy statement relating to our 2019 annual meeting of stockholders, filed with the SEC on April 5, 2019;
- our Current Reports on Form 8-K filed with the SEC on January 7, 2019, January 14, 2019, June 3, 2019 and June 19, 2019; and
- the description of our common stock in our registration statement on Form 8-A filed with the SEC on September 25, 2014.

We also incorporate by reference any future filings (other than current reports furnished under Item 2.02 or Item 7.01 of Form 8-K and exhibits filed on such form that are related to such items unless such Form 8-K expressly provides to the contrary) made with the SEC pursuant to Sections 13(a), 13(c), 14 or 15(d) of the Exchange Act, including those made after the date of the initial filing of the registration statement of which this prospectus supplement is a part and prior to effectiveness of such registration statement, until we file a post-effective amendment that indicates the termination of the offering of the shares of our common stock made by this prospectus supplement and will become a part of this prospectus supplement from the date that such documents are filed with the SEC. Information in such future filings updates and supplements the information provided in this prospectus supplement. Any statements in any such future filings will automatically be deemed to modify and supersede any information in any document we previously filed with the SEC that is incorporated or deemed to be incorporated herein by reference to the extent that statements in the later filed document modify or replace such earlier statements.

You can request a copy of these filings, at no cost, by writing or telephoning us at the following address or telephone number:

Calithera Biosciences, Inc.
343 Oyster Point Blvd. Suite 200
South San Francisco, California 94080
(650) 870-1000
Attn: Secretary

Table of Contents

PROSPECTUS

$250,000,000

Common Stock

From time to time, we may offer and sell up to an aggregate amount of $250,000,000 of shares of our common stock.

We will provide the specific terms of these offerings in one or more supplements to this prospectus. We may also authorize one or more free writing prospectuses to be provided to you in connection with these offerings. The prospectus supplement and any related free writing prospectus may also add, update or change information contained in this prospectus. You should carefully read this prospectus, the applicable prospectus supplement and any related free writing prospectus, as well as any documents incorporated by reference, before buying any of the shares of common stock being offered.

Our common stock is listed on the Nasdaq Global Select Market under the trading symbol “CALA.” On August 7, 2017, the last reported sale price of our common stock was $14.95 per share. The applicable prospectus supplement will contain information, where applicable, as to other listings, if any, on the Nasdaq Global Select Market or other securities exchange of the shares of common stock covered by the applicable prospectus supplement.

Investing in shares of our common stock involves a high degree of risk. You should review carefully the risks and uncertainties described under the section titled “Risk Factors” on page 8 of this prospectus and any similar section contained in the applicable prospectus supplement and in any free writing prospectuses we have authorized for use in connection with a specific offering, and under similar headings in the documents that are incorporated by reference into this prospectus.

This prospectus may not be used to consummate a sale of shares of our common stock unless accompanied by a prospectus supplement.

The shares of our common stock may be sold directly by us to investors, through agents designated from time to time or to or through underwriters or dealers, on a continuous or delayed basis. For additional information on the methods of sale, you should refer to the section titled “Plan of Distribution” in this prospectus. If any agents or underwriters are involved in the sale of any shares of our common stock with respect to which this prospectus is being delivered, the names of such agents or underwriters and any applicable fees, commissions, discounts and overallotment options will be set forth in a prospectus supplement. The price to the public of such shares of our common stock and the net proceeds we expect to receive from such sale will also be set forth in a prospectus supplement.

Neither the Securities and Exchange Commission nor any state securities commission has approved or disapproved of these securities or determined if this prospectus is truthful or complete. Any representation to the contrary is a criminal offense.

The date of this prospectus is August 18, 2017.

TABLE OF CONTENTS

ABOUT THIS PROSPECTUS

This prospectus is part of a registration statement on Form S-3 that we filed with the Securities and Exchange Commission, or the SEC, using a “shelf” registration process. Under this shelf registration statement, we may, from time to time, offer and sell in one or more offerings, up to a total dollar amount of $250,000,000 of shares of our common stock as described in this prospectus.

Each time we offer shares of our common stock under this prospectus, we will provide a prospectus supplement that will contain more specific information about the terms of that offering. We may also authorize one or more free writing prospectuses to be provided to you that may contain material information relating to these offerings. The prospectus supplement and any related free writing prospectus that we may authorize to be provided to you may also add, update or change any of the information contained in this prospectus or in the documents that we have incorporated by reference into this prospectus. We urge you to read carefully this prospectus, any applicable prospectus supplement and any free writing prospectuses we have authorized for use in connection with a specific offering, together with the information incorporated herein by reference as described under the heading “Incorporation of Certain Information by Reference,” before buying any of the shares of our common stock being offered.

This prospectus may not be used to consummate a sale of shares of our common stock unless it is accompanied by a prospectus supplement.

You should rely only on the information contained in, or incorporated by reference into, this prospectus and any applicable prospectus supplement, along with the information contained in any free writing prospectuses we have authorized for use in connection with a specific offering. We have not authorized anyone to provide you with any information other than that contained or incorporated by reference in this prospectus and any applicable prospectus supplement, along with the information contained in any free writing prospectuses we have authorized for use in connection with a specific offering. You must not rely upon any information or representation not contained or incorporated by reference in this prospectus, the accompanying prospectus supplement or in any related free writing prospectus that we may authorize to be provided to you. We take no responsibility for, and can provide no assurance as to the reliability of, any other information that others may give you. This prospectus is an offer to sell only the shares of our common stock offered hereby, but only under circumstances and in jurisdictions where it is lawful to do so.

The information appearing in this prospectus, any applicable prospectus supplement or any related free writing prospectus is accurate only as of the date on the front of the document and that any information we have incorporated by reference is accurate only as of the date of the document

incorporated by reference, regardless of the time of delivery of this prospectus, any applicable prospectus supplement or any related free writing prospectus, or any sale of shares of our common stock. Our business, financial condition, results of operations and prospects may have changed since those dates.

This prospectus contains and incorporates by reference market data and industry statistics and forecasts that are based on independent industry publications and other publicly available information. Although we believe that these sources are reliable, we do not guarantee the accuracy or completeness of this information and we have not independently verified this information. Although we are not aware of any misstatements regarding the market and industry data presented in this prospectus and the documents incorporated herein by reference, these estimates involve risks and uncertainties and are subject to change based on various factors, including those discussed under the section titled “Risk Factors” contained in the applicable prospectus supplement and any related free writing prospectus, and under similar headings in the other documents that are incorporated by reference into this prospectus. Accordingly, investors should not place undue reliance on this information.

This prospectus contains summaries of certain provisions contained in some of the documents described herein, but reference is made to the actual documents for complete information. All of the summaries are qualified in their entirety by the actual documents. Copies of some of the documents referred to herein have been filed, will be filed or will be incorporated by reference as exhibits to the registration statement of which this prospectus is a part, and you may obtain copies of those documents as described below under the section titled “Where You Can Find Additional Information.”

PROSPECTUS SUMMARY

This summary highlights selected information contained elsewhere in this prospectus or incorporated by reference in this prospectus, and does not contain all of the information that you need to consider in making your investment decision. You should carefully read the entire prospectus, the applicable prospectus supplement and any related free writing prospectus, including the risks of investing in our shares of our common stock discussed under the section titled "Risk Factors" contained in the applicable prospectus supplement and any related free writing prospectus, and under similar headings in the other documents that are incorporated by reference into this prospectus. You should also carefully read the other information incorporated by reference into this prospectus, including our financial statements, and the exhibits to the registration statement of which this prospectus is a part.

Calithera Biosciences, Inc.

Overview

We are a clinical-stage pharmaceutical company focused on discovering and developing novel small molecule oncology drugs directed against tumor and immune cell targets that control key metabolic pathways in the tumor microenvironment. Tumor metabolism and immuno-oncology (I-O) have emerged as promising new fields for cancer drug discovery, and recent clinical successes with therapeutic agents in each field have demonstrated the potential to create fundamentally new therapies for cancer patients. We are developing agents that take advantage of the unique metabolic requirements of tumor cells and cancer-fighting immune cells such as cytotoxic T-cells. Our lead product candidate, CB-839, is an internally discovered, first-in-class oral inhibitor of glutaminase, a critical enzyme in tumor cells. CB-839 administered as a single agent has resulted in clinical responses in renal cell cancer and acute myeloid leukemia. We are currently enrolling patients in a randomized, double blind, placebo controlled Phase 2 trial in renal cell carcinoma (RCC) and a Phase 2 trial in triple negative breast cancer (TNBC). We are also enrolling patients in a series of combination Phase 1/2 cohorts in specific solid tumor types including a trial in combination with cabozantinib in RCC patients, and a trial in combination with nivolumab in RCC, melanoma and non-small cell lung cancer patients. CB-839 has been very well tolerated both as a single agent and in combination with other therapies. Our second product candidate, CB-1158, is a first-in-class oral inhibitor of arginase, an enzyme that depletes the amino acid arginine, a key metabolic nutrient for T-cells, and is being co-developed with Incyte Corporation (Incyte) for hematology and oncology indications. CB-1158, also known as INCB001158, is currently being tested in a Phase 1 clinical trial in patients with solid tumors as a single agent and in combination with a PD-1 inhibitor. We also have ongoing research efforts that are focused on discovering additional product candidates against novel tumor metabolism and immunology targets.

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

CB-839 may also have the potential to work in combination with immuno-oncology therapeutics. Inhibition of glutaminase results in accumulation of glutamine, the substrate of glutaminase, in tumors. Glutamine, which is frequently depleted in the tumor microenvironment due to avid uptake by tumor cells, has been shown to be an important nutrient for T-cell proliferation. Administration of CB-839 to tumor-bearing animals substantially enhances the anti-tumor activity of checkpoint inhibitors, potentially by restoring the levels of glutamine in the tumor microenvironment and thereby enabling T-cells to proliferate. Checkpoint inhibitors, including the approved agents nivolumab (marketed as Opdivo) and pembrolizumab (marketed as Keytruda), are a class of immuno-oncology agents directed against programmed death protein-1 (PD-1) or programmed death ligand-1 (PD-L1) that promote the activation and tumor-killing properties of the patient's own immune cells, such as cytotoxic T-cells. CB-839 could potentially have multiple mechanisms of action in the treatment of cancer first by starving the tumor cell, and second by facilitating the activation of T-cells in the nutrient-deprived tumor microenvironment.

CB-1158 is a potent and selective orally bioavailable inhibitor of the enzyme arginase that was discovered at Calithera and is being co-developed with Incyte. 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 myeloid immune cells known as myeloid-derived suppressor cells (MDSCs), plays an important role in halting T-cell proliferation. But in many tumors, including lung, gastrointestinal, bladder, renal cancer and acute myeloid leukemia, arginase-expressing myeloid cells accumulate and maintain an immunosuppressive environment, blocking the ability of T-cells and NK-cells to kill cancer cells. We believe that inhibitors of arginase can promote an anti-tumor immune response by restoring arginine levels, thereby allowing activation of the body's own immune cells, including cytotoxic T-cells and NK-cells.

CB-839

Our lead product candidate, CB-839 is a potent, selective, reversible and orally bioavailable inhibitor of human glutaminase. CB-839 binds to a unique site on glutaminase that is distinct from the site that binds glutamine, thereby reducing the potential for undesirable side effects due to inhibition of other enzymes and receptors that bind glutamine. CB-839 takes advantage of the pronounced dependency many cancers have on the nutrient glutamine for growth and survival. In preclinical studies, CB-839 demonstrated broad antitumor activity in cell lines, inhibited the growth of human tumors in animal models, and was well tolerated in animals at doses above those shown to inhibit tumor growth. CB-839 was also synergistic with several approved cancer therapeutics that are part of the current standard of care.

Renal Cell Carcinoma

CB-839 is being developed for the treatment of patients with RCC. In 2017, RCC is estimated to be diagnosed in 63,990 people in the United States, according to the National Cancer Institute. We evaluated CB-839 as a monotherapy in a RCC cohort in the dose expansion stage of our solid tumor Phase 1 clinical trial CX-839-001. As of December 31, 2016, 20 efficacy-evaluable RCC patients were treated with single agent CB-839 on the BID (twice-daily) dosing schedule. One patient achieved a partial response with a substantial decrease in target lesions (32%), including a dramatic improvement in the patient's extensive lymphadenopathy. A total of 10 patients (50%) showed stable disease or better.

We are also evaluating CB-839 in expansion cohorts in combination with everolimus and cabozantinib. In November 2016, we presented data on 15 evaluable RCC patients, including 12 clear

cell patients, and three papillary patients. Ninety-three percent (93%) of these patients had disease control (response or stable disease); one patient had a partial response, one patient had progressive disease, and 13 patients had stable disease. The median progression free survival was 8.5 months and for the majority of patients, their time on therapy is longer than their time on treatment in their prior therapy. In the clear cell patient population the disease control rate was 100% and eight patients remain on study. Patients enrolled in the trial had advanced or metastatic disease and had received a median of two prior treatments, which included tyrosine kinase inhibitors, mTOR inhibitors, and checkpoint inhibitors. Patients were administered CB-839 in oral doses that ranged from 400-800 mg twice a day in combination with a fixed oral dose of everolimus at 10 mg once a day. The addition of CB-839 to full-dose everolimus has been well tolerated, with a similar safety profile to the known profile of everolimus alone. Grade 3 events include two events of hyperglycemia and one event each of diarrhea, anemia and fatigue. We plan to present additional data from this trial in the first quarter of 2018. In addition, we continue to enroll patients in single arm cohort of patients dosed with CB-839 in combination with cabozantinib, with data expected in 2018.

In August 2017, we initiated CX-839-005, a Phase 2 randomized, double blind, placebo controlled trial designed to evaluate the safety and efficacy of CB-839 in combination with everolimus versus placebo with everolimus in approximately 250 patients with metastatic, clear cell RCC patients who have been treated with at least two prior lines of systemic therapy including a vascular endothelial growth factor receptor-targeting tyrosine kinase inhibitor and at least one of either cabozantinib or an active PD-1/PD-L1 inhibitor. Patients will be randomized in a 2:1 ratio. The primary endpoint is progression free survival assessed by an independent review committee; overall survival will be assessed as a secondary endpoint. The multicenter, international study will be conducted at multiple sites in the United States, Europe and Canada. The U.S. Food and Drug Administration (FDA) has granted Fast Track designation to CB-839 in combination with everolimus, for the treatment of patients with metastatic RCC who have received 2 or more prior lines of therapy.

In August 2016, we initiated CX-839-004, a Phase 1/2 clinical trial of CB-839 in combination with the PD-1 inhibitor nivolumab in patients with RCC, melanoma, and non-small cell lung cancer. The Phase 1/2 study will assess the safety, pharmacokinetics and pharmacodynamics of CB-839 and nivolumab. The study will enroll patients who are either naïve to checkpoint inhibitors, had prior nivolumab therapy, or were recently treated with nivolumab without tumor response. Patients may be progressing on nivolumab or failing to respond and will receive CB-839 as an “add-on” therapy. In December 2016, we announced a clinical trial collaboration to evaluate Bristol-Myers Squibb’s nivolumab in combination with CB-839 in two of the cohorts of patients with clear cell RCC. In May 2017, the collaboration with Bristol-Myers Squibb was expanded to include additional RCC cohorts as well as non-small cell lung cancer and melanoma (all study patients). We expect to present initial data from this trial in the fourth quarter of 2017.

Triple Negative Breast Cancer

In December 2016, we presented data on 28 TNBC patients treated with doses of CB-839 of 400, 600 or 800 mg BID in combination with 80 mg/m^2 IV paclitaxel, weekly, three weeks out of four; 23 were evaluable for response. The majority of patients had received at least three prior lines of therapy, with 43% of patients treated with five or more prior therapies in the advanced/metastatic setting. Most patients had received prior taxane therapy in either the neo-adjuvant or metastatic setting. Among evaluable patients treated with CB-839 doses of at least 600 mg BID (n=16), there are 5 partial responses (31%) and disease control in 11 patients (69%). In addition, the combination overcame resistance to paclitaxel in heavily pretreated TNBC patients. There was a 38% response rate and 50% disease control rate in patients who received prior taxanes in the metastatic setting. There was a 50%

response rate among taxane-refractory African American patients. Four of five responding patients were African American. This is consistent with higher glutamine utilization observed in tumors from this population. CB-839 was well tolerated in combination with paclitaxel.

In July 2017, we initiated CX-839-007, a Phase 2 trial of CB-839 with paclitaxel in TNBC patients. Four single arm, open label, cohorts of African American and non-African American patients will be treated in both the early stage setting, where patients have no prior taxane treatment, as well as the late stage setting after prior taxane. The primary endpoint of this trial is objective response rate. We plan to present data from the TNBC development program in the fourth quarter of 2017, with additional data to be presented in 2018.

Colorectal Cancer

In 2017, an estimated 135,000 new cases of colorectal cancer (CRC) will be diagnosed in the United States according to the American Cancer Society. Researchers report that PIK3CA mutation is present in 10% to 20% of all cases of CRC. An academic research group at Case Western demonstrated that single agent CB-839 inhibits the growth of CRCs with PIK3CA mutations in immunocompromised mice, but CRC tumors with a normal PIK3CA gene were not inhibited. Remarkably, the combination of CB-839 with 5-florouracil induced complete and long-lasting tumor regressions in animals bearing PIK3CA mutant CRC tumors, but not tumors with normal PIK3CA, suggesting that this combinational therapy may be a unique and effective approach in the clinic. In the third quarter of 2016, an investigator-sponsored clinical trial was initiated by Drs. Jennifer Eads, Alok Khorana, and Neal Meropol at the Case Western Comprehensive Cancer Center. Enrollment in this study is ongoing.

CB-1158

Our second product candidate, CB-1158, is a first-in-class immuno-oncology metabolic checkpoint inhibitor targeting arginase, an immunosuppressive enzyme in MDSCs responsible for T-cell suppression. Significant infiltration by arginase-expressing myeloid cells has been observed in many solid tumor types including lung, colorectal esophageal, bladder, head and neck, kidney cancer, and other tumor types. We have confirmed that arginase-expressing MDSCs are found by immunohistochemistry in a wide range of tumor types including non-small cell lung (both adenocarcinoma and squamous types), gastrointestinal and bladder cancers. CB-1158 is being co-developed with Incyte.

CB-1158 entered clinical trials in September 2016, and is currently being tested in a Phase 1 clinical trial in patients with solid tumors. We presented data in June 2017 at the American Society of Clinical Oncology (ASCO) annual meeting. As of the data cut off of April 24, 2017, a total of 17 patients with advanced solid tumors had received single agent doses ranging from 50 to 150 mg twice a day (BID) in the ongoing Phase 1 trial. CB-1158 was generally well tolerated with no drug-related serious adverse events. Treatment related adverse events were limited to one case each of Grade 1 anemia, fatigue, increased ALT and myalgia. No Grade 3 treatment-related adverse events were reported. Reversible, asymptomatic elevations of urinary orotic acid, a highly sensitive marker of urea cycle inhibition, were observed in two patients at 150 mg BID. Plasma levels of arginase were inhibited > 90% in all patients, and in 10 of 11 patients plasma arginine increased 1.5-fold or more. The pharmacokinetics support BID dosing of CB-1158, as currently tested doses continuously maintained targeted levels of arginase inhibition. The trial is continuing to enroll patients in the dose escalation phase of the study, and expansion cohorts in pre-defined tumor types, to be followed by combination studies with an anti-PD-1 antibody.

In January 2017, we entered into a global collaboration and license agreement for the research, development and commercialization of our small molecule arginase inhibitor CB-1158 in hematology and oncology with Incyte, or the Incyte Collaboration Agreement. We are collaborating with Incyte on and co-funding the development of CB-1158 for oncology and hematology indications. Incyte bears 70% and we bear 30% of global development costs, unless we opt out of development co-funding. We have the right to conduct a portion of clinical development studies under the collaboration, including combination studies of a licensed product with any other of our proprietary compounds. If we do not opt out of development co-funding, the parties will share profits and losses in the United States, with 60% to Incyte and 40% to us, and we have the right to co-detail licensed products in the United States. We retain the rights to certain arginase inhibitors for specific indications outside of hematology and oncology. In the first quarter of 2017 Incyte paid us an upfront license fee of $45.0 million and in March 2017, we achieved a development milestone of $12.0 million for which we received payment in May of 2017. Incyte may pay potential development, regulatory and sales milestone payments up to an additional $418.0 million if the profit share is in effect, or an additional $738.0 million if the profit share terminates.

Risks Associated with our Business

Our business is subject to numerous risks and uncertainties, including those highlighted in the section titled “Risk Factors” immediately following this prospectus 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 had an accumulated deficit of $133.3 million as of June 30, 2017.
- We will need substantial additional funding and may be unable to raise capital when needed, which would force us to delay, reduce or eliminate our product development programs or commercialization efforts.
- Our approach to discovery and development of product candidates that target tumor metabolism and tumor immunology is unproven and may never lead to marketable products.
- We are very early in our development efforts, which may not be successful.
- 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.
- 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.
- 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.
- Our arginase inhibitors program in hematology and oncology indications, including CB-1158, is reliant in part on Incyte for the successful development and commercialization in a timely manner. If Incyte does not devote sufficient resources to CB-1158’s development, is

unsuccessful in its efforts, or chooses to terminate its agreement with us, our business, operating results and financial condition will be harmed.

- If we are alleged to infringe intellectual property rights of third parties, our business could be harmed.
- 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.
- We face substantial competition from major pharmaceutical companies, specialty pharmaceutical companies and biotechnology companies worldwide.

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.

In addition, we are an "emerging growth company" as defined in the Jumpstart Our Business Startups Act, or the JOBS Act, enacted in April 2012, and therefore we take advantage of certain exemptions from various public company reporting requirements, including not being required to have our internal control over financial reporting audited by our independent registered public accounting firm pursuant to Section 404(b) of the Sarbanes-Oxley Act of 2002, reduced disclosure obligations regarding executive compensation in our periodic reports and proxy statement and exemptions from the requirements of holding a nonbinding advisory vote on executive compensation and any golden parachute payments not previously approved. We may take advantage of these exemptions until the earlier of the fifth anniversary of the closing of our initial public offering in October 2014 or until we are no longer an "emerging growth company."

Corporate Information

We were incorporated in Delaware in March 2010 as Protein Activation Therapeutics, Inc. and subsequently changed our name to Calithera Biosciences, Inc. Our headquarters are located at 343 Oyster Point Blvd., Suite 200, South San Francisco, California 94080, and our telephone number is (650) 870-1000. Our website address is www.calithera.com. The information contained on, or that can be accessed through, our website is not part of, and is not incorporated by reference into this prospectus and should not be considered to be part of this prospectus. Investors should not rely on any such information in deciding whether to purchase our common stock.

"Calithera," the Calithera logo and other trademarks or service marks of Calithera Biosciences, Inc. appearing in this prospectus are the property of Calithera Biosciences, Inc. Other trademarks, service marks or trade names appearing in this prospectus are the property of their respective owners. We do not intend our use or display of other companies' trade names, trademarks or service marks to imply a relationship with, or endorsement or sponsorship of us by, these other companies.

The Shares of Common Stock We May Offer

We may offer shares of our common stock up to a total dollar amount of $250,000,000, from time to time under this prospectus, together with the applicable prospectus supplement and any related free writing prospectus, at prices and on terms to be determined by market conditions at the time of any

offering. Each time we offer shares of our common stock under this prospectus, we will provide a prospectus supplement that will describe the specific amounts, prices and other important terms of the offering.

The applicable prospectus supplement and any related free writing prospectus that we may authorize to be provided to you may also add, update or change any of the information contained in this prospectus or in the documents we have incorporated by reference. However, no prospectus supplement or free writing prospectus will offer any security other than shares of our common stock.

THIS PROSPECTUS MAY NOT BE USED TO CONSUMMATE A SALE OF SHARES OF OUR COMMON STOCK UNLESS IT IS ACCOMPANIED BY A PROSPECTUS SUPPLEMENT.

We may sell the shares of our common stock directly to investors or to or through agents, underwriters or dealers. We and our agents or underwriters, reserve the right to accept or reject all or part of any proposed purchase of shares of our common stock. If we do offer shares of our common stock to or through agents or underwriters, we will include in the applicable prospectus supplement:

- the names of those agents or underwriters;
- applicable fees, discounts and commissions to be paid to them;
- details regarding overallotment options, if any; and
- the net proceeds to us.

We may issue shares of our common stock from time to time. The holders of our common stock are entitled to one vote for each share held of record on all matters submitted to a vote of stockholders. Subject to preferences that may be applicable to any outstanding shares of preferred stock, the holders of common stock are entitled to receive ratably such dividends as may be declared by our board of directors out of legally available funds. Upon our liquidation, dissolution or winding up, holders of our common stock are entitled to share ratably in all assets remaining after payment of liabilities and the liquidation preferences of any outstanding shares of preferred stock. Holders of common stock have no preemptive rights and no right to convert their common stock into any other securities. There are no redemption or sinking fund provisions applicable to our common stock. We urge you to read the applicable prospectus supplement (and any related free writing prospectus that we may authorize to be provided to you) related to any common stock being offered.

Use of Proceeds

Except as described in any applicable prospectus supplement or in any free writing prospectuses we have authorized for use in connection with a specific offering, we currently intend to use the net proceeds from the sale of the shares of our common stock offered by us hereunder, if any, for working capital, capital expenditures and other general corporate purposes. See “Use of Proceeds” in this prospectus.

Nasdaq Global Select Market Listing

Our common stock is listed on the Nasdaq Global Select Market under the symbol “CALA.” The applicable prospectus supplement will contain information, where applicable, as to other listings, if any, on the Nasdaq Global Select Market or other securities exchange of the shares of our common stock covered by the applicable prospectus supplement.

RISK FACTORS

Investing in shares of our common stock involves a high degree of risk. Before deciding whether to invest in shares of our common stock, you should consider carefully the risks and uncertainties described under the section titled "Risk Factors" contained in the applicable prospectus supplement and any related free writing prospectus, and discussed under the section titled "Risk Factors" contained in our most recent Annual Report on Form 10-K and in our most recent Quarterly Report on Form 10-Q, as well as any amendments thereto reflected in subsequent filings with the SEC, which are incorporated by reference into this prospectus in their entirety, together with other information in this prospectus, the documents incorporated by reference and any free writing prospectus that we may authorize for use in connection with this offering. The risks described in these documents are not the only ones we face, but those that we consider to be material. There may be other unknown or unpredictable economic, business, competitive, regulatory or other factors that could have material adverse effects on our future results. Past financial performance may not be a reliable indicator of future performance, and historical trends should not be used to anticipate results or trends in future periods. If any of these risks actually occurs, our business, financial condition, results of operations or cash flow could be harmed. This could cause the trading price of our common stock to decline, resulting in a loss of all or part of your investment. Please also read carefully the section below titled "Special Note Regarding Forward-Looking Statements."

SPECIAL NOTE REGARDING FORWARD-LOOKING STATEMENTS

This prospectus and the documents we have filed with the SEC that are incorporated by reference contain "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, or the Exchange Act. These statements relate to future events or to our future operating or financial performance and involve known and unknown risks, uncertainties and other factors which may cause our actual results, performance or achievements to be materially different from any future results, performances or achievements expressed or implied by the forward-looking statements. Forward-looking statements may include, but are not limited to, statements about:

- our ability to fund our working capital requirements;
- our ability to obtain and maintain regulatory approval of our product candidates;
- our ability to successfully commercialize our product candidates;
- the rate and degree of market acceptance of our products that are approved;
- our estimates of our expenses, ongoing losses, future revenue, capital requirements and our needs for or ability to obtain additional financing;
- our expectation that our existing capital resources and the net proceeds from this offering will be sufficient to enable us to complete our planned clinical trials;
- our expectations with respect to the Incyte Collaboration Agreement;
- our ability to obtain and maintain intellectual property protection for our product candidates;
- our ability to identify and develop new product candidates;
- our ability to retain and recruit key personnel;
- our use of proceeds from this offering;
- our financial performance; and
- developments and projections relating to our competitors or our industry.

These risks are not exhaustive. Other sections of this prospectus may include additional factors that could harm our business and financial performance. Moreover, we operate in a very competitive and rapidly changing environment. New risk factors emerge from time to time, and it is not possible for our management to predict all risk factors nor can we assess the impact of all factors on our business or the extent to which any factor, or combination of factors, may cause actual results to differ materially from those contained in, or implied by, any forward-looking statements.

All statements other than statements of historical facts contained in this prospectus, including statements regarding our future financial condition, business strategy and plans, and objectives of management for future operations, are forward-looking statements. In some cases, you can identify forward-looking statements by words such as "anticipate," "believe," "continue," "could," "design," "estimate," "expect," "intend," "may," "plan," "potentially," "predict," "should," "will" or the negative of these terms or other similar expressions. These statements reflect our current views with respect to future events and are based on assumptions and are subject to risks and uncertainties. Given these uncertainties, you should not place undue reliance on these forward-looking statements. We discuss in greater detail many of these risks under the section titled "Risk Factors" contained in the applicable prospectus supplement, in any free writing prospectuses we may authorize for use in connection with a specific offering, and in our most recent Annual Report on Form 10-K and in our most recent Quarterly Report on Form 10-Q, as well as any amendments thereto reflected in subsequent filings with the SEC,

which are incorporated by reference into this prospectus in their entirety. Also, these forward-looking statements represent our estimates and assumptions only as of the date of the document containing the applicable statement. Unless required by law, we undertake no obligation to update or revise any forward-looking statements to reflect new information or future events or developments. You should read this prospectus, any applicable prospectus supplement, together with the documents we have filed with the SEC that are incorporated by reference and any free writing prospectus that we may authorize for use in connection with this offering completely and with the understanding that our actual future results may be materially different from what we expect. We qualify all of the forward-looking statements in the foregoing documents by these cautionary statements.

In addition, statements that “we believe” and similar statements reflect our beliefs and opinions on the relevant subject. These statements are based upon information available to us as of the date of this prospectus, and while we believe such information forms a reasonable basis for such statements, such information may be limited or incomplete, and our statements should not be read to indicate that we have conducted an exhaustive inquiry into, or review of, all potentially available relevant information. These statements are inherently uncertain and investors are cautioned not to unduly rely upon these statements.

USE OF PROCEEDS

Except as described in any applicable prospectus supplement or in any free writing prospectuses we have authorized for use in connection with a specific offering, we currently intend to use the net proceeds from this offering for working capital and general corporate purposes, which may include, among other things, funding research and development, clinical trials, vendor payables, potential regulatory submissions, hiring additional personnel and capital expenditures.

DESCRIPTION OF CAPITAL STOCK

Our authorized capital stock consists of 200,000,000 shares of common stock, par value $0.0001 per share, and 10,000,000 shares of preferred stock, par value $0.0001 per share. The following is a summary of the rights of our common and preferred stock and some of the provisions of our amended and restated certificate of incorporation and amended and restated bylaws, an investor rights agreement between us and certain stockholders and Delaware General Corporation Law. This is only a summary, and is qualified in its entirety by reference to our certificate of incorporation, investor rights agreement and the bylaws.

Common Stock

Voting Rights

Each holder of common stock is entitled to one vote for each share on all matters submitted to a vote of the stockholders. The affirmative vote of holders of at least a majority of the voting power of all of the then-outstanding shares of capital stock, voting as a single class, is required to amend certain provisions of our amended and restated certificate of incorporation, including provisions relating to amending our amended and restated bylaws, the classified board, the size of our board, removal of directors, director liability, vacancies on our board, special meetings, stockholder notices, actions by written consent and exclusive jurisdiction.

Dividends

Subject to preferences that may apply to any outstanding preferred stock, holders of our common stock are entitled to receive ratably any dividends that our board of directors may declare out of funds legally available for that purpose on a non-cumulative basis.

Liquidation

In the event of our liquidation, dissolution or winding up, holders of our common stock are entitled to share ratably in all assets remaining after payment of liabilities and the liquidation preference of any outstanding preferred stock.

Rights and Preferences

Holders of our common stock have no preemptive, conversion, subscription or other rights, and there are no redemption or sinking fund provisions applicable to our common stock. The rights, preferences and privileges of the holders of our common stock are subject to and may be adversely affected by the rights of the holders of shares of any series of our preferred stock that we may designate in the future.

Preferred Stock

Our board of directors has the authority, without further action by our stockholders, to issue up to 10,000,000 shares of preferred stock in one or more series and to fix the number, rights, preferences, privileges and restrictions thereof. These rights, preferences and privileges could include dividend rights, conversion rights, voting rights, terms of redemption, liquidation preferences and sinking fund terms, and the number of shares constituting any series or the designation of such series, any or all of which may be greater than the rights of common stock. The issuance of our preferred stock could adversely affect the voting power of holders of common stock and the likelihood that such holders will receive dividend payments and payments upon liquidation. In addition, the issuance of preferred stock could have the effect of delaying, deferring or preventing a change of control or other corporate action. We have no current plan to issue any shares of preferred stock.

Stockholder Registration Rights

Certain holders of shares of our common stock, including certain holders of five percent of our capital stock and entities affiliated with certain of our directors, are entitled to certain rights with respect to registration of such shares under the Securities Act. These shares are referred to as registrable securities. The holders of these registrable securities possess registration rights pursuant to the terms of the investor rights agreement and are described in additional detail below.

The registration of shares of our common stock pursuant to the exercise of the registration rights described below would enable the holders to trade these shares without restriction under the Securities Act when the applicable registration statement is declared effective. We will pay the registration expenses, other than underwriting discounts, selling commissions and stock transfer taxes, of the shares registered pursuant to the demand, piggyback and Form S-3 registrations described below.

Generally, in an underwritten offering, the managing underwriter, if any, has the right, subject to specified conditions, to limit the number of shares the holders may include. The demand, piggyback and Form S-3 registration rights described below will expire three years after the effective date of the registration statement, of which this prospectus forms a part, or, with respect to any particular holder, at such time that such holder can sell its shares under Rule 144 of the Securities Act during any three-month period.

Demand Registration Rights

The holders of the registrable securities are entitled to certain demand registration rights. The holders of at least 60% of the registrable securities may make a written request that we register all or a portion of their shares, subject to certain specified exceptions. Such request for registration must cover securities the aggregate offering price of which, before payment of underwriting discounts and commissions, would exceed $50,000,000.

Piggyback Registration Rights

In connection with the filing of the registration statement of which this prospectus forms a part, the holders of registrable securities were entitled to, and the necessary percentage of holders waived, their rights to include their shares of registrable securities in the registration statement of which this prospectus forms a part. If we propose to register for offer and sale any of our securities under the Securities Act in another offering, either for our own account or for the account of other security holders, the holders of these shares will be entitled to certain “piggyback” registration rights allowing them to include their shares in such registration, subject to certain marketing and other limitations. As a result, whenever we propose to file a registration statement under the Securities Act, including a registration statement on Form S-3 as discussed below, other than with respect to a demand registration or a registration statement on Forms S-4 or S-8 or related to stock issued upon conversion of debt securities, the holders of these shares are entitled to notice of the registration and have the right, subject to limitations that the underwriters may impose on the number of shares included in the registration, to include their shares in the registration.

Form S-3 Registration Rights

The holders of the registrable securities are entitled to certain Form S-3 registration rights. Any holder of these shares can make a request that we register for offer and sale their shares on Form S-3 if we are qualified to file a registration statement on Form S-3, subject to certain specified exceptions. Such request for registration on Form S-3 must cover securities the aggregate offering price of which, before payment of the underwriting discounts and commissions, equals or exceeds $5,000,000. We will not be required to effect more than two registrations on Form S-3 within any 12 month period.

Anti-Takeover Provisions of Delaware Law and Our Charter Documents

Section 203 of the Delaware General Corporation Law

We are subject to Section 203 of the Delaware General Corporation Law, which prohibits a Delaware corporation from engaging in any business combination with any interested stockholder for a period of three years after the date that such stockholder became an interested stockholder, with the following exceptions:

- before such date, the board of directors of the corporation approved either the business combination or the transaction that resulted in the stockholder becoming an interested stockholder;
- upon completion of the transaction that resulted in the stockholder becoming an interested stockholder, the interested stockholder owned at least 85% of the voting stock of the corporation outstanding at the time the transaction began, excluding for purposes of determining the voting stock outstanding (but not the outstanding voting stock owned by the interested stockholder) those shares owned (1) by persons who are directors and also officers and (2) employee stock plans in which employee participants do not have the right to determine confidentially whether shares held subject to the plan will be tendered in a tender or exchange offer; and
- on or after such date, the business combination is approved by the board of directors and authorized at an annual or special meeting of the stockholders, and not by written consent, by the affirmative vote of at least 66⅔% of the outstanding voting stock that is not owned by the interested stockholder.

In general, Section 203 defines a “business combination” to include the following:

- any merger or consolidation involving the corporation and the interested stockholder;
- any sale, transfer, pledge or other disposition of 10% or more of the assets of the corporation involving the interested stockholder;
- subject to certain exceptions, any transaction that results in the issuance or transfer by the corporation of any stock of the corporation to the interested stockholder;
- any transaction involving the corporation that has the effect of increasing the proportionate share of the stock or any class or series of the corporation beneficially owned by the interested stockholder; and
- the receipt by the interested stockholder of the benefit of any loans, advances, guarantees, pledges or other financial benefits by or through the corporation.

In general, Section 203 defines an “interested stockholder” as an entity or person who, together with the person’s affiliates and associates, beneficially owns, or within three years prior to the time of determination of interested stockholder status owned, 15% or more of the outstanding voting stock of the corporation.

The statute could prohibit or delay mergers or other takeover or change in control attempts and, accordingly, may discourage attempts to acquire us even though such a transaction may offer our stockholders the opportunity to sell their stock at a price above the prevailing market price.

Amended and Restated Certificate of Incorporation and Amended and Restated Bylaws

Among other things, our amended and restated certificate of incorporation and amended and restated bylaws:

- permit our board of directors to issue up to 10,000,000 shares of preferred stock, with any rights, preferences and privileges as they may designate, including the right to approve an acquisition or other change of control;
- provide that the authorized number of directors may be changed only by resolution of our board of directors;
- provide that our board of directors will be classified into three classes of directors;
- provide that, subject to the rights of any series of preferred stock to elect directors, directors may only be removed for cause, which removal may be effected, subject to any limitation imposed by law, by the holders of at least a majority of the voting power of all of our then-outstanding shares of the capital stock entitled to vote generally at an election of directors;
- provide that all vacancies, including newly created directorships, may, except as otherwise required by law, be filled by the affirmative vote of a majority of directors then in office, even if less than a quorum;
- require that any action to be taken by our stockholders must be effected at a duly called annual or special meeting of stockholders and not be taken by written consent or electronic transmission;
- provide that stockholders seeking to present proposals before a meeting of stockholders or to nominate candidates for election as directors at a meeting of stockholders must provide advance notice in writing, and also specify requirements as to the form and content of a stockholder's notice;
- provide that special meetings of our stockholders may be called only by the chairman of our board of directors, our chief executive officer or by our board of directors pursuant to a resolution adopted by a majority of the total number of authorized directors; and
- not provide for cumulative voting rights, therefore allowing the holders of a majority of the shares of common stock entitled to vote in any election of directors to elect all of the directors standing for election, if they should so choose.

The amendment of any of these provisions would require approval by the holders of at least 66 2/3% of the voting power of all of our then-outstanding common stock entitled to vote generally in the election of directors, voting together as a single class.

The combination of these provisions will make it more difficult for our existing stockholders to replace our board of directors as well as for another party to obtain control of us by replacing our board of directors. Since our board of directors has the power to retain and discharge our officers, these provisions could also make it more difficult for existing stockholders or another party to effect a change in management. In addition, the authorization of undesignated preferred stock makes it possible for our board of directors to issue preferred stock with voting or other rights or preferences that could impede the success of any attempt to change our control.

These provisions are intended to enhance the likelihood of continued stability in the composition of our board of directors and its policies and to discourage coercive takeover practices and inadequate takeover bids. These provisions are also designed to reduce our vulnerability to hostile takeovers and to discourage certain tactics that may be used in proxy fights. However, such provisions could have the effect of discouraging others from making tender offers for our shares and may have the effect of

delaying changes in our control or management. As a consequence, these provisions may also inhibit fluctuations in the market price of our stock that could result from actual or rumored takeover attempts. We believe that the benefits of these provisions, including increased protection of our potential ability to negotiate with the proponent of an unfriendly or unsolicited proposal to acquire or restructure our company, outweigh the disadvantages of discouraging takeover proposals, because negotiation of takeover proposals could result in an improvement of their terms.

Choice of Forum

Our amended and restated certificate of incorporation provides that the Court of Chancery of the State of Delaware will be 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 certificate of incorporation or our bylaws; or any action asserting a claim against us that is governed by the internal affairs doctrine. The enforceability of similar choice of forum provisions in other companies' certificates of incorporation has been challenged in legal proceedings, and it is possible that, in connection with one or more actions or proceedings described above, a court could find the choice of forum provisions contained in our certificate of incorporation to be inapplicable or unenforceable.

Listing

Our common stock is listed on the Nasdaq Global Select Market under the symbol "CALA."

Transfer Agent and Registrar

The transfer agent and registrar for our common stock is American Stock Transfer & Trust Company, LLC. The transfer agent's address is 6201 15th Avenue, Brooklyn, New York 11219.

PLAN OF DISTRIBUTION

We may sell the shares of our common stock from time to time pursuant to underwritten public offerings, direct sales to the public, negotiated transactions, block trades or a combination of these methods. We may sell the shares of our common stock to or through underwriters or dealers, through agents, or directly to one or more purchasers. We may distribute the shares from time to time in one or more transactions:

- at a fixed price or prices, which may be changed;
- at market prices prevailing at the time of sale;
- at prices related to such prevailing market prices; or
- at negotiated prices.

A prospectus supplement or supplements (and any related free writing prospectus that we may authorize to be provided to you) will describe the terms of the offering of the shares of our common stock, including, to the extent applicable:

- the name or names of the underwriters, if any;
- the purchase price of the shares of our common stock or other consideration therefor, and the proceeds, if any, we will receive from the sale;
- any over-allotment options under which underwriters may purchase additional shares of our common stock from us;
- any agency fees or underwriting discounts and other items constituting agents' or underwriters' compensation;
- any public offering price;
- any discounts or concessions allowed or reallowed or paid to dealers; and
- any securities exchange or market on which the shares of our common stock may be listed.

Only underwriters named in the prospectus supplement will be underwriters of the shares of our common stock offered by the prospectus supplement.

If underwriters are used in the sale, they will acquire the shares of our common stock for their own account and may resell the shares of our common stock from time to time in one or more transactions at a fixed public offering price or at varying prices determined at the time of sale. The obligations of the underwriters to purchase the shares of our common stock will be subject to the conditions set forth in the applicable underwriting agreement. We may offer the shares of our common stock to the public through underwriting syndicates represented by managing underwriters or by underwriters without a syndicate. Subject to certain conditions, the underwriters will be obligated to purchase all of the shares of our common stock offered by the prospectus supplement, other than shares of our common stock covered by any over-allotment option. Any public offering price and any discounts or concessions allowed or reallowed or paid to dealers may change from time to time. We may use underwriters with whom we have a material relationship. We will describe in the prospectus supplement, naming the underwriter, the nature of any such relationship.

We may sell shares of our common stock directly or through agents we designate from time to time. We will name any agent involved in the offering and sale of shares of our common stock and we will describe any commissions we will pay the agent in the prospectus supplement. Unless the prospectus supplement states otherwise, our agent will act on a best-efforts basis for the period of its appointment.

We may authorize agents or underwriters to solicit offers by certain types of institutional investors to purchase shares of our common stock from us at the public offering price set forth in the prospectus supplement pursuant to delayed delivery contracts providing for payment and delivery on a specified date in the future. We will describe the conditions to these contracts and the commissions we must pay for solicitation of these contracts in the prospectus supplement.

We may provide agents and underwriters with indemnification against civil liabilities, including liabilities under the Securities Act, or contribution with respect to payments that the agents or underwriters may make with respect to these liabilities. Agents and underwriters may engage in transactions with, or perform services for us in the ordinary course of business.

Any underwriter may engage in over-allotment, stabilizing transactions, short-covering transactions and penalty bids in accordance with Regulation M under the Exchange Act. Over-allotment involves sales in excess of the offering size, which create a short position. Stabilizing transactions permit bids to purchase the underlying security so long as the stabilizing bids do not exceed a specified maximum price. Syndicate-covering or other short-covering transactions involve purchases of the shares of our common stock, either through exercise of the over-allotment option or in the open market after the distribution is completed, to cover short positions. Penalty bids permit the underwriters to reclaim a selling concession from a dealer when the shares of our common stock originally sold by the dealer are purchased in a stabilizing or covering transaction to cover short positions. Those activities may cause the price of the shares of our common stock to be higher than it would otherwise be. If commenced, the underwriters may discontinue any of the activities at any time.

Any underwriters or agents that are qualified market makers on the Nasdaq Global Select Market may engage in passive market making transactions in our common stock on the Nasdaq Global Select Market accordance with Regulation M under the Exchange Act, during the business day prior to the pricing of the offering, before the commencement of offers or sales of the common stock. Passive market makers must comply with applicable volume and price limitations and must be identified as passive market makers. In general, a passive market maker must display its bid at a price not in excess of the highest independent bid for such security; if all independent bids are lowered below the passive market maker’s bid, however, the passive market maker’s bid must then be lowered when certain purchase limits are exceeded. Passive market making may stabilize the market price of the shares of our common stock at a level above that which might otherwise prevail in the open market and, if commenced, may be discontinued at any time.

LEGAL MATTERS

Cooley LLP, Palo Alto, California will pass upon the validity of the shares of common stock offered hereby. As of the date of this prospectus, GC&H Investments, LLC and GC&H Investments, entities comprised of partners and associates of Cooley LLP, beneficially own an aggregate of 2,378 shares of our common stock. Additional legal matters may be passed upon for us or any underwriters, dealers or agents, by counsel that we name in the applicable prospectus supplement.

EXPERTS

Ernst & Young LLP, independent registered public accounting firm, has audited our financial statements included in our Annual Report on Form 10-K for the year ended December 31, 2016, as set forth in their report, which is incorporated by reference in this prospectus and elsewhere in the registration statement. Our financial statements are incorporated by reference in reliance on Ernst & Young LLP's report, given on their authority as experts in accounting and auditing.

WHERE YOU CAN FIND ADDITIONAL INFORMATION

This prospectus is part of the registration statement on Form S-3 we filed with the SEC under the Securities Act and does not contain all the information set forth in the registration statement. Whenever a reference is made in this prospectus to any of our contracts, agreements or other documents, the reference may not be complete and you should refer to the exhibits that are a part of the registration statement or the exhibits to the reports or other documents incorporated by reference into this prospectus for a copy of such contract, agreement or other document. Because we are subject to the information and reporting requirements of the Exchange Act, we file annual, quarterly and current reports, proxy statements and other information with the SEC. Our SEC filings are available to the public over the Internet at the SEC's website at http://www.sec.gov. You may also read and copy any document we file at the SEC's Public Reference Room at 100 F Street, N.E., Washington, D.C. 20549. Please call the SEC at 1-800-SEC-0330 for further information on the operation of the Public Reference Room.

INCORPORATION OF CERTAIN INFORMATION BY REFERENCE

The SEC allows us to "incorporate by reference" information from other documents that we file with it, which means that we can disclose important information to you by referring you to those documents. The information incorporated by reference is considered to be part of this prospectus. Information in this prospectus supersedes information incorporated by reference that we filed with the SEC prior to the date of this prospectus, while information that we file later with the SEC will automatically update and supersede the information in this prospectus. We incorporate by reference into this prospectus and the registration statement of which this prospectus is a part the information or documents listed below that we have filed with the SEC (Commission File No. 001-36644):

- our Annual Report on Form 10-K for the year ended December 31, 2016, filed with the SEC on March 16, 2017;
- our Quarterly Report on Form 10-Q for the quarter ended March 31, 2017, filed with the SEC on May 9, 2017;
- our Quarterly Report on Form 10-Q for the quarter ended June 30, 2017, filed with the SEC on August 8, 2017;
- the information specifically incorporated by reference in our Annual Report on Form 10-K for the year ended December 31, 2016, from our definitive proxy statement relating to our 2017 annual meeting of stockholders, filed with the SEC on April 21, 2017;

- our Current Reports on Form 8-K filed with the SEC on January 27, 2017, March 13, 2017, March 22, 2017, May 15, 2017 and June 14, 2017; and
- the description of our common stock in our registration statement on Form 8-A filed with the SEC on September 25, 2014.

All filings filed by us pursuant to the Exchange Act after the date of the initial filing of the registration statement of which this prospectus is a part and prior to effectiveness of the registration statement shall be deemed to be incorporated by reference into this prospectus.

We also incorporate by reference any future filings (other than current reports furnished under Item 2.02 or Item 7.01 of Form 8-K and exhibits filed on such form that are related to such items unless such Form 8-K expressly provides to the contrary) made with the SEC pursuant to Sections 13(a), 13(c), 14 or 15(d) of the Exchange Act, including those made after the date of the initial filing of the registration statement of which this prospectus is a part and prior to effectiveness of such registration statement, until we file a post-effective amendment that indicates the termination of the offering of the shares of our common stock made by this prospectus and will become a part of this prospectus from the date that such documents are filed with the SEC. Information in such future filings updates and supplements the information provided in this prospectus. Any statements in any such future filings will automatically be deemed to modify and supersede any information in any document we previously filed with the SEC that is incorporated or deemed to be incorporated herein by reference to the extent that statements in the later filed document modify or replace such earlier statements.

You can request a copy of these filings, at no cost, by writing or telephoning us at the following address or telephone number:

Calithera Biosciences, Inc.
343 Oyster Point Blvd. Suite 200
South San Francisco, California 94080
(650) 870-1000
Attn: Secretary

$50,000,000

Common Stock

PROSPECTUS SUPPLEMENT

Jefferies

December 6, 2019