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

Prospectus Supplement
(To Prospectus Dated August 18, 2017)

12,500,000 Shares

Common Stock

We are offering 12,500,000 shares of our common stock.

Our common stock is listed on the Nasdaq Global Select Market under the symbol "CALA." On June 18, 2019, the closing price of our common stock on the Nasdaq Global Select Market was $4.74 per share.

Investing in our common stock involves a high degree of risk. See "Risk Factors" on page S-6 of this prospectus supplement as well as those contained in the documents incorporated herein.

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

We are an "emerging growth company" under the federal securities laws and are subject to reduced public company reporting requirements.

	Per Share	Total
Public offering price	$ 4.00	$50,000,000
Underwriting discounts and commissions(1)	$ 0.24	$ 3,000,000
Proceeds to Calithera Biosciences, Inc. before expenses	$ 3.76	$47,000,000

(1) See "Underwriting" for additional disclosure regarding underwriting compensation.

We have granted the underwriters an option for a period of 30 days from the date of this prospectus supplement to purchase up to 1,875,000 additional shares of our common stock from us at the public offering price, less underwriting discounts and commissions.

The underwriters expect to deliver the shares to purchasers on or about June 21, 2019.

Joint Book-Running Managers

SVB Leerink **Wells Fargo Securities** **William Blair**

The date of this prospectus supplement is June 18, 2019.

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PROSPECTUS SUPPLEMENT

PROSPECTUS

You should rely only on the information contained in or incorporated by reference in this prospectus supplement, the accompanying prospectus and in any free writing prospectus that we have authorized for use in connection with this offering. We have not, and the underwriters have not, authorized anyone to provide you with information that is different. We and the underwriters are offering to sell shares of common stock and seeking offers to buy shares of common stock only in jurisdictions where offers and sales are permitted. The information appearing in this prospectus supplement, the accompanying prospectus, the documents incorporated by reference in this prospectus supplement and the accompanying prospectus, and in any free writing prospectus that we have authorized for use in connection with this offering, is accurate only as of the date of those respective documents, regardless of the time of delivery of those respective documents or sale of our common stock.

For investors outside the United States: we have not, and the underwriters have not, done anything that would permit this offering or possession or distribution of this prospectus supplement, the accompanying prospectus and in any free writing prospectus that we have authorized for use in connection with this offering in any jurisdiction where action for that purpose is required, other than in the United States. Persons outside the United States who come into possession of this prospectus supplement, the accompanying prospectus and any free writing prospectus that we have authorized for use in connection with this offering must inform themselves about, and observe any restrictions relating to, the offering of the shares of common stock and the distribution of this prospectus supplement, the accompanying prospectus and any free writing prospectus that we have authorized for use in connection with this offering outside the United States.

ABOUT THIS PROSPECTUS SUPPLEMENT

This document consists of two parts. The first part is this prospectus supplement, which describes the terms of this offering of common stock and also adds to and updates information contained in the accompanying prospectus and the documents incorporated by reference into this prospectus supplement. The second part is the accompanying prospectus dated August 18, 2017, which includes the documents incorporated by reference therein and provides more general information. To the extent the information contained in this prospectus supplement differs or varies from the information contained in the accompanying prospectus or the documents incorporated by reference herein or therein, you should rely on the information in this prospectus supplement. Generally, when we refer to the prospectus, we are referring to this prospectus supplement and the accompanying prospectus combined. You should read both this prospectus supplement and the accompanying prospectus, together with additional information described in the section titled "Where You Can Find More Information."

"Calithera," the Calithera logo and other trademarks or service marks of Calithera Biosciences, Inc. appearing in this prospectus supplement are the property of Calithera Biosciences, Inc. Other trademarks, service marks or trade names appearing in this prospectus supplement 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.

PROSPECTUS SUPPLEMENT SUMMARY

This summary highlights certain information about us, this offering and selected information contained elsewhere in or incorporated by reference into this prospectus supplement. This summary provides an overview of selected information and does not contain all of the information you should consider before deciding whether to invest in our common stock. Therefore, you should read the entire prospectus supplement and the accompanying prospectus carefully (including the documents incorporated by reference herein and therein), especially the "Risk Factors" section on page S-6 and in the documents incorporated by reference and our financial statements and the related notes incorporated by reference in this prospectus supplement and the accompanying prospectus, before deciding to invest in our common stock. Unless the context otherwise requires, we use the terms "Calithera," "Company," "we," "us" and "our" in this prospectus supplement and the accompanying prospectus to refer to Calithera Biosciences, Inc.

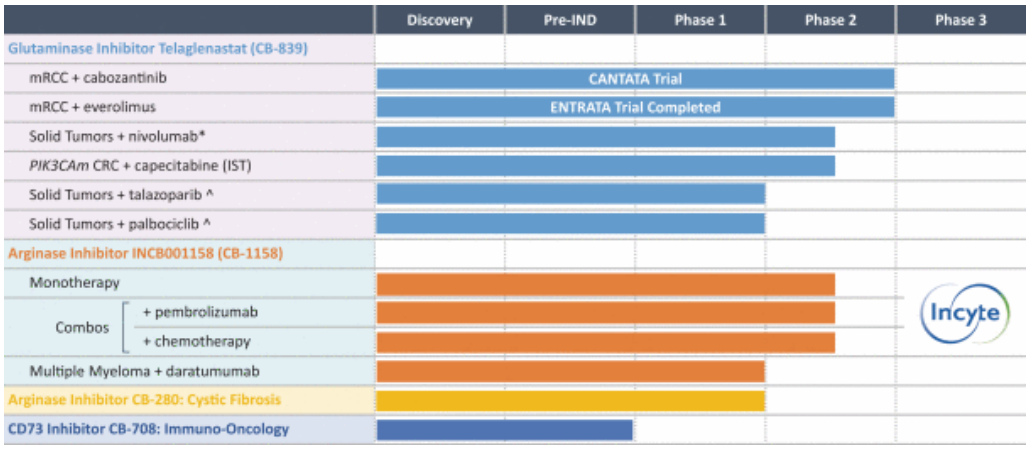
Overview

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 four 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 four product candidates in our development pipeline.

Our lead product candidate telaglenastat is an oral inhibitor of glutaminase, a critical enzyme in tumor cells that controls utilization of the nutrient glutamine. 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. 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 – the ENTRATA trial and the CANTATA trial. 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.

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. Data from INCB001158 is expected to be presented at a medical meeting in the second half of 2019. Arginase inhibitors also have potential in the treatment of cystic fibrosis; accordingly, we have selected CB-280, a unique oral arginase inhibitor, to enter clinical trials in cystic fibrosis patients. In February 2019, we initiated a Phase 1 trial to evaluate the safety, tolerability and pharmacokinetic profile of oral CB-280 in healthy volunteers. We anticipate completion of this study in 2019. Our candidate CB-708 targets CD73, an enzyme in the tumor microenvironment that produces adenosine, a powerful inhibitor of immune function in tumors. We anticipate that our oral CD73 inhibitor will also enter the clinic in 2019.

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



Recent Developments

Telaglenastat (CB-839) – Top-line Results of ENTRATA Trial

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.

In June 2019, we presented top-line results from the ENTRATA trial. Patients enrolled were heavily pre-treated with a median of three prior lines of therapy for advanced metastatic disease including 70% with two or more prior TKIs, and 68% with intermediate/poor MSKCC prognostic score. Eighty-eight percent of patients received prior PD-1/PD-L1 therapy. Telaglenastat, when added to everolimus, doubled the median PFS to 3.8 months as compared to 1.9 months for everolimus alone and reduced the risk of disease progression or death by 36% (HR=0.64, p=0.079 one-sided). The primary endpoint of the trial was PFS per investigator assessment with a predetermined threshold of p≤0.2 one-sided. 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 □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%). We intend to present the data at an upcoming medical meeting.

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 should not be considered to be part of this prospectus supplement. Investors should not rely on any such information in deciding whether to purchase our common stock.

JOBS Act

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."

The Offering

Common Stock offered by us	12,500,000 shares
Common Stock to be outstanding immediately after this offering	51,583,053 shares (or 53,458,053 shares if the underwriters exercise their option to purchase additional shares in full)
Option to purchase additional shares	The underwriters have a 30-day option to purchase up to an additional 1,875,000 shares of common stock.
Use of Proceeds	We estimate the net proceeds from this offering will be approximately $46.7 million (or approximately $53.8 million if the underwriters exercise in full their option to purchase an additional 1,875,000 shares), based on the public offering price of $4.00 per share, after deducting underwriting discounts and commissions and estimated offering expenses payable by us. We intend to use the net proceeds from this offering to fund our clinical trials and for working capital and general corporate purposes. See the section titled "Use of Proceeds" for a more complete description of the intended use of proceeds from this offering.
Risk Factors	See "Risk Factors" on page S-6 and other information included and incorporated by reference in this prospectus supplement and the accompanying prospectus for a discussion of factors that you should carefully consider before deciding to invest in our common stock.
Nasdaq Global Select Symbol	"CALA"

The number of shares of common stock to be outstanding after this offering is based on 39,083,053 shares of common stock outstanding as of March 31, 2019, and excludes:

- 6,488,540 shares of common stock issuable upon the exercise of outstanding stock options as of March 31, 2019, with a weighted-average exercise price of $6.95 per share;
- 259,446 shares 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
- 687,904 shares of common stock 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.

Subsequent to March 31, 2019, and through the date of this prospectus supplement:

- we granted stock options to purchase 176,000 shares of common stock under our 2014 Equity Incentive Plan with a weighted average exercise price of $5.67 per share;
- we issued and sold an aggregate of 150,064 shares of common stock at an average price of $6.71 per share pursuant to our at-the-market offering program; and

- we issued and sold an aggregate of 91,881 shares of common stock at a price of $4.11 per share pursuant to our 2014 Employee Stock Purchase Plan.

Unless otherwise indicated, all information in this prospectus supplement does not include the additional share issuances and shares reserved for future issuance subsequent to March 31, 2019 as set forth above, and further assumes:

- no exercise of the underwriters' option to purchase additional shares of common stock; and
- no exercise of outstanding stock options.

RISK FACTORS

You should consider carefully the risks described below and discussed in the section titled "Risk Factors" contained in our Annual Report on Form 10-K for the year ended December 31, 2018 and Quarterly Report on Form 10-Q for the three months ended March 31, 2019, 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 in their entirety, together with other information in this prospectus supplement, and the information and documents incorporated by reference in this prospectus supplement, 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 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."

Risks Related to This Offering

We have broad discretion in the use of the net proceeds from this offering and may not use them effectively.

Our management will have broad discretion in the application of the net proceeds from this offering and could spend the proceeds in ways that do not improve our business, financial condition or results of operations or enhance the value of our common stock. 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.

The failure by our management to apply these funds effectively could result in financial losses that could harm our business, cause the price of our common stock to decline and delay the development of our product candidates. Pending their use, we may invest the net proceeds from this offering in a manner that does not produce income or that loses value.

Purchasers in this offering will experience immediate and substantial dilution in the tangible net book value of their investment.

If you purchase our common stock in this offering, you will incur an immediate dilution of $1.04 in net tangible book value per share from the price you paid, based on the public offering price of $4.00 per share. The exercise of outstanding options will result in further dilution. For a further description of the dilution that you will experience immediately after this offering, see the section titled "Dilution."

SPECIAL NOTE REGARDING FORWARD-LOOKING STATEMENTS

This prospectus supplement, 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;
- our expectations with respect to our global collaboration and license agreement with Incyte;
- 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 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 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, 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" herein, and in our most recent Annual Report on Form 10-K and 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 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, 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.

Although we believe that the expectations reflected in the forward-looking statements are reasonable, we cannot guarantee future results, levels of activity, performance or achievements. These forward-looking statements are made as of the date of this prospectus supplement and we disclaim any intention and have no obligation or responsibility, except as required by law, to update or revise any forward-looking statements, whether as a result of new information, future events or otherwise.

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

We estimate that we will receive net proceeds from the sale of 12,500,000 shares of common stock in this offering of approximately $46.7 million (or approximately $53.8 million if the underwriters exercise in full their option to purchase an additional 1,875,000 shares) at the public offering price of $4.00 per share and after deducting underwriting discounts and commissions and estimated offering expenses payable by us.

We currently estimate that we will use the net proceeds from this offering, together with our cash, cash equivalents and investments, as follows:

- to further the clinical development of telaglenastat, our glutaminase inhibitor, including manufacturing activities to support an NDA application and potentially initiate an additional clinical trial;
- to fund our share of development costs of CB-1158, our arginase inhibitor in oncology, as it advances into later stage clinical trials with our collaboration partner, Incyte Corporation;
- to fund clinical development activities related to our additional clinical candidates, CB-280, an arginase inhibitor for cystic fibrosis, and CB-708, our CD73 inhibitor, as well as to fund early stage research; and
- for working capital and other general corporate purposes, which may include the acquisition or licensing of other products, businesses or technologies.

However, due to the uncertainties inherent in the product development process, it is difficult to estimate with certainty the exact amounts of the net proceeds from this offering that may be used for the above purposes. Our management will have broad discretion over the use of the net proceeds from this offering. The amounts and timing of our expenditures will depend upon numerous factors including the results of our research and development efforts, the timing and success of preclinical studies and any ongoing clinical trials or clinical trials we may commence in the future, the timing of regulatory submissions and the amount of cash obtained through future collaborations, if any.

We believe opportunities may exist from time to time to expand our current business through acquisitions or in-licenses of complementary companies, medicines or technologies. While we have no current agreements, commitments or understandings for any specific acquisitions or in-licenses at this time, we may use a portion of the net proceeds for these purposes.

Pending the use of the proceeds from this offering as described above, we intend to invest the net proceeds in interest-bearing investment-grade securities or government securities.

DIVIDEND POLICY

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

CAPITALIZATION

The following table sets forth our cash, cash equivalents and investments and capitalization as of March 31, 2019:

- on an actual basis; and
- on an as adjusted basis to reflect the sale by us of 12,500,000 shares of common stock in this offering at the public offering price of $4.00 per share and after deducting underwriting discounts and commissions and estimated offering expenses payable by us.

The following information should be read in conjunction with the section titled "Management's Discussion and Analysis of Financial Condition and Results of Operations" and financial statements and related notes in our most recent Annual Report on Form 10-K and Quarterly Report on Form 10-Q and other documents incorporated by reference in this prospectus supplement and the accompanying prospectus. For more details on how you can obtain our periodic reports and other information, see the section titled "Where You Can Find More Information" in this prospectus supplement.

	As of March 31, 2019	
	Actual	As Adjusted
	(in thousands, except share and per share data)	
Cash, cash equivalents and investments	$ 116,999	$ 163,699
Stockholders' equity:		
Preferred stock, $0.0001 par value, 10,000,000 shares authorized, no shares issued and outstanding, actual and as adjusted	$ —	$ —
Common stock, $0.0001 par value, 200,000,000 shares authorized, 39,083,053 shares issued and outstanding, actual; 51,583,053 shares issued and outstanding, as adjusted	4	5
Additional paid-in capital	325,905	372,604
Accumulated deficit	(219,928)	(219,928)
Accumulated other comprehensive loss	(7)	(7)
Total stockholders' equity	105,974	152,674
Total capitalization	$ 105,974	$ 152,674

The number of shares of common stock to be outstanding after this offering is based on 39,083,053 shares of common stock outstanding as of March 31, 2019, and excludes:

- 6,488,540 shares of common stock issuable upon the exercise of outstanding stock options as of March 31, 2019, with a weighted-average exercise price of $6.95 per share;
- 259,446 shares 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
- 687,904 shares of common stock 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.

Subsequent to March 31, 2019, and through the date of this prospectus supplement:

- we granted stock options to purchase 176,000 shares of common stock under our 2014 Equity Incentive Plan with a weighted average exercise price of $5.67 per share;

- we issued and sold an aggregate of 150,064 shares of common stock at an average price of $6.71 per share pursuant to our at-the-market offering program; and
- we issued and sold an aggregate of 91,881 shares of common stock at a price of $4.11 per share pursuant to our 2014 Employee Stock Purchase Plan.

The above table and discussion does not include the additional share issuances and shares reserved for future issuance subsequent to March 31, 2019 as set forth above.

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 March 31, 2019, was $106.0 million, or $2.71 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 12,500,000 shares common stock in this offering at the public offering price of $4.00 per share, and after deducting underwriting discounts and commissions and estimated offering expenses payable by us, our net tangible book value as of March 31, 2019, would have been $152.7 million, or $2.96 per share of common stock. This represents an immediate increase in net tangible book value of $0.25 per share to our existing stockholders and immediate dilution in net tangible book value of $1.04 per share to investors participating in this offering. The following table illustrates this dilution per share to investors participating in this offering:

Public offering price per share		$4.00
Historical net tangible book value per share at March 31, 2019	$2.71	
Increase per share attributable to new investors	0.25	
As adjusted net tangible book value per share after giving effect to this offering		2.96
Dilution in adjusted net tangible book value per share to new investors		$1.04

If the underwriters exercise in full their option to purchase an additional 1,875,000 shares of our common stock at the public offering price of $4.00 per share, the as adjusted net tangible book value per share after giving effect to this offering would be $2.99 per share, representing an immediate increase to existing stockholders of $0.28 per share, and immediate dilution in as adjusted net tangible book value of $1.01 per share to investors participating in this offering.

The number of shares of common stock to be outstanding after this offering is based on 39,083,053 shares of common stock outstanding as of March 31, 2019, and excludes:

- 6,488,540 shares of common stock issuable upon the exercise of outstanding stock options as of March 31, 2019, with a weighted-average exercise price of $6.95 per share;
- 259,446 shares 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
- 687,904 shares of common stock 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.

Subsequent to March 31, 2019, and through the date of this prospectus supplement:

- we granted stock options to purchase 176,000 shares of common stock under our 2014 Equity Incentive Plan with a weighted average exercise price of $5.67 per share;
- we issued and sold an aggregate of 150,064 shares of common stock at an average price of $6.71 per share pursuant to our at-the-market offering program; and
- we issued and sold an aggregate of 91,881 shares of common stock at a price of $4.11 per share pursuant to our 2014 Employee Stock Purchase Plan.

The above table and discussion does not include the additional share issuances and shares reserved for future issuance subsequent to March 31, 2019 as set forth above.

To the extent that options are exercised, new options are issued under our equity incentive plans, or we issue additional shares of common stock in the future, there will be further dilution to investors participating in this offering.

MATERIAL U.S. FEDERAL INCOME TAX CONSEQUENCES TO NON-U.S. HOLDERS

The following summary describes the material U.S. federal income tax consequences of the acquisition, ownership, and disposition of our common stock acquired in this offering by Non-U.S. Holders (as defined below). This discussion is not a complete analysis of all potential U.S. federal income tax consequences relating thereto, and does not deal with foreign, state, and local consequences that may be relevant to Non-U.S. Holders in light of their particular circumstances, nor does it address U.S. federal tax consequences (such as gift and estate taxes) other than income taxes. Special rules different from those described below may apply to certain Non-U.S. Holders that are subject to special treatment under the Internal Revenue Code of 1986, as amended (the "Code"), such as financial institutions, insurance companies, tax-exempt organizations, broker-dealers and traders in securities, U.S. expatriates, "controlled foreign corporations," "passive foreign investment companies," corporations that accumulate earnings to avoid U.S. federal income tax, corporations organized outside of the United States, any state thereof or the District of Columbia that are nonetheless treated as U.S. taxpayers for U.S. federal income tax purposes, persons that hold our common stock as part of a "straddle," "hedge," "conversion transaction," "synthetic security" or integrated investment or other risk reduction strategy, persons who acquire our common stock through the exercise of an option or otherwise as compensation, persons subject to the alternative minimum tax or federal Medicare contribution tax on net investment income, persons subject to special tax accounting rules under Section 451(b) of the Code, "qualified foreign pension funds" as defined in Section 897(l)(2) of the Code and entities all of the interests of which are held by qualified foreign pension funds, partnerships and other pass-through entities or arrangements, and investors in such pass-through entities or arrangements. Such Non-U.S. Holders are urged to consult their own tax advisors to determine the U.S. federal, state, local, and other tax consequences that may be relevant to them. Furthermore, the discussion below is based upon the provisions of the Code, and Treasury Regulations, rulings, and judicial decisions thereunder as of the date hereof, and such authorities may be repealed, revoked, or modified, perhaps retroactively, so as to result in U.S. federal income tax consequences different from those discussed below. We have not requested a ruling from the U.S. Internal Revenue Service (the "IRS") with respect to the statements made and the conclusions reached in the following summary, and there can be no assurance that the IRS will agree with such statements and conclusions. This discussion assumes that the Non-U.S. Holder holds our common stock as a "capital asset" within the meaning of Section 1221 of the Code (generally, property held for investment).

This discussion is for informational purposes only and is not tax advice. Persons considering the purchase of our common stock pursuant to this offering should consult their own tax advisors concerning the U.S. federal income, estate, and other tax consequences of acquiring, owning, and disposing of our common stock in light of their particular situations as well as any consequences arising under the laws of any other taxing jurisdiction, including any state, local, or foreign tax consequences.

For the purposes of this discussion, a "Non-U.S. Holder" is, for U.S. federal income tax purposes, a beneficial owner of common stock that is neither a U.S. Holder, nor a partnership (or other entity treated as a partnership for U.S. federal income tax purposes regardless of its place of organization or formation). A "U.S. Holder" means a beneficial owner of our common stock that is for U.S. federal income tax purposes any of the following:

- an individual who is a citizen or resident of the United States;
- a corporation or other entity treated as a corporation for U.S. federal income tax purposes created or organized in or under the laws of the United States, any state thereof, or the District of Columbia;
- an estate the income of which is subject to U.S. federal income taxation regardless of its source; or
- a trust if it (1) is subject to the primary supervision of a court within the United States and one or more U.S. persons have the authority to control all substantial decisions of the trust or (2) has a valid election in effect under applicable U.S. Treasury Regulations to be treated as a U.S. person.

Distributions

Distributions, if any, made on our common stock to a Non-U.S. Holder to the extent made out of our current or accumulated earnings and profits (as determined under U.S. federal income tax principles) generally will constitute dividends for U.S. tax purposes and will be subject to withholding tax at a 30% rate or such lower rate as may be specified by an applicable income tax treaty, subject to the discussions below regarding effectively connected income, backup withholding, and foreign accounts. To obtain a reduced rate of withholding under a treaty, a Non-U.S. Holder generally will be required to provide us with a properly executed IRS Form W-8BEN (in the case of individuals) or IRS Form W-8BEN-E (in the case of entities), or other appropriate form, certifying the Non-U.S. Holder's entitlement to benefits under that treaty. This certification must be provided to us or our paying agent prior to the payment of dividends and must be updated periodically. In the case of a Non-U.S. Holder that is an entity, Treasury Regulations and the relevant tax treaty provide rules to determine whether, for purposes of determining the applicability of a tax treaty, dividends will be treated as paid to the entity or to those holding an interest in that entity. If a Non-U.S. Holder holds stock through a financial institution or other agent acting on the holder's behalf, the holder will be required to provide appropriate documentation to such agent. The holder's agent will then be required to provide certification to us or our paying agent, either directly or through other intermediaries. If you are eligible for a reduced rate of U.S. federal withholding tax under an income tax treaty and you do not timely file the required certification, you may be able to obtain a refund or credit of any excess amounts withheld by timely filing an appropriate claim for a refund with the IRS.

We generally are not required to withhold tax on dividends paid to a Non-U.S. Holder that are effectively connected with the Non-U.S. Holder's conduct of a trade or business within the United States (and, if required by an applicable income tax treaty, are attributable to a permanent establishment or fixed base that such holder maintains in the United States) if a properly executed IRS Form W-8ECI, stating that the dividends are so connected, is furnished to us (or, if stock is held through a financial institution or other agent, to such agent). In general, such effectively connected dividends will be subject to U.S. federal income tax, on a net income basis at the regular rates applicable to U.S. residents. A corporate Non-U.S. Holder receiving effectively connected dividends may also be subject to an additional "branch profits tax," which is imposed, under certain circumstances, at a rate of 30% (or such lower rate as may be specified by an applicable treaty) on the corporate Non-U.S. Holder's effectively connected earnings and profits, subject to certain adjustments. Non-U.S. Holders should consult their tax advisors regarding any applicable income tax treaties that may provide for different rules.

To the extent distributions on our common stock, if any, exceed our current and accumulated earnings and profits, they will first reduce the Non-U.S. Holder's adjusted basis in our common stock, but not below zero, and then will be treated as gain to the extent of any excess amount distributed, and taxed in the same manner as gain realized from a sale or other disposition of common stock as described in the next section.

Gain on Disposition of Our Common Stock

Subject to the discussions below regarding backup withholding and foreign accounts, a Non-U.S. Holder generally will not be subject to U.S. federal income tax with respect to gain realized on a sale or other disposition of our common stock unless (a) the gain is effectively connected with a trade or business of such holder in the United States (and, if required by an applicable income tax treaty, is attributable to a permanent establishment or fixed base that such holder maintains in the United States), (b) the Non-U.S. Holder is a nonresident alien individual and is present in the United States for 183 or more days in the taxable year of the disposition and certain other conditions are met, or (c) we are or have been a "United States real property holding corporation" within the meaning of Code Section 897(c)(2) at any time within the shorter of the five-year period preceding such disposition or such holder's holding period. In general, we would be a United States real property holding corporation if our interests in U.S. real estate comprise (by fair market value) at least half of our business assets. We believe that we have not been and we are not, and do not anticipate becoming, a United States real property holding corporation. Even if we are treated as a United States real property holding corporation, gain realized by a Non-U.S. Holder on a disposition of our common stock will not be subject to U.S. federal income tax so long as

(1) the Non-U.S. Holder owned, directly, indirectly and constructively, no more than 5% of our common stock at all times within the shorter of (i) the five-year period preceding the disposition or (ii) the holder's holding period and (2) our common stock is regularly traded on an established securities market. There can be no assurance that our common stock will continue to qualify as regularly traded on an established securities market. If any gain on your disposition is taxable because we are a United States real property holding corporation and your ownership of our common stock exceeds 5%, you will be taxed on such disposition generally in the manner as gain that is effectively connected with the conduct of a U.S. trade or business (subject to the provisions under an applicable income tax treaty), except that the branch profits tax generally will not apply.

If you are a Non-U.S. Holder described in (a) above, you will be required to pay tax on the net gain derived from the sale at regular U.S. federal income tax rates, and corporate Non-U.S. Holders described in (a) above may be subject to the additional branch profits tax at a 30% rate or such lower rate as may be specified by an applicable income tax treaty. Gain described in (b) above will be subject to U.S. federal income tax at a flat 30% rate or such lower rate as may be specified by an applicable income tax treaty, which gain may be offset by certain U.S.-source capital losses (even though you are not considered a resident of the United States), provided that the Non-U.S. Holder has timely filed U.S. federal income tax returns with respect to such losses.

Information Reporting Requirements and Backup Withholding

Generally, we must report information to the IRS with respect to any dividends we pay on our common stock (even if the payments are exempt from withholding), including the amount of any such dividends, the name and address of the recipient, and the amount, if any, of tax withheld. A similar report is sent to the holder to whom any such dividends are paid. Pursuant to tax treaties or certain other agreements, the IRS may make its reports available to tax authorities in the recipient's country of residence.

Dividends paid by us (or our paying agents) to a Non-U.S. Holder may also be subject to U.S. backup withholding. U.S. backup withholding generally will not apply to a Non-U.S. Holder who provides a properly executed IRS Form W-8BEN, IRS Form W-8BEN-E, or IRS Form W-ECI, or otherwise establishes an exemption. Notwithstanding the foregoing, backup withholding may apply if the payor has actual knowledge, or reason to know, that the holder is a U.S. person who is not an exempt recipient.

U.S. information reporting and backup withholding requirements generally will apply to the proceeds of a disposition of our common stock effected by or through a U.S. office of any broker, U.S. or foreign, except that information reporting and such requirements may be avoided if the holder provides a properly executed IRS Form W-8BEN or IRS Form W-8BEN-E or otherwise meets documentary evidence requirements for establishing non-U.S. person status or otherwise establishes an exemption. Generally, U.S. information reporting and backup withholding requirements will not apply to a payment of disposition proceeds to a Non-U.S. Holder where the transaction is effected outside the United States through a non-U.S. office of a non-U.S. broker. Information reporting and backup withholding requirements may, however, apply to a payment of disposition proceeds if the broker has actual knowledge, or reason to know, that the holder is, in fact, a U.S. person. For information reporting purposes, certain brokers with substantial U.S. ownership or operations will generally be treated in a manner similar to U.S. brokers.

Backup withholding is not an additional tax. Any amounts withheld under the backup withholding rules may be credited against the tax liability of persons subject to backup withholding, provided that the required information is timely furnished to the IRS.

Foreign Accounts

Sections 1471 through 1474 of the Code (commonly referred to as FATCA) impose a U.S. federal withholding tax of 30% on certain payments, including dividends paid on, and the gross proceeds of a disposition of, our common stock paid to a foreign financial institution (as specifically defined by applicable rules) unless

such institution enters into an agreement with the U.S. government to withhold on certain payments and to collect and provide to the U.S. tax authorities substantial information regarding U.S. account holders of such institution (which includes certain equity holders of such institution, as well as certain account holders that are foreign entities with U.S. owners). FATCA also generally imposes a federal withholding tax of 30% on certain payments, including dividends paid on, and the gross proceeds of a disposition of, our common stock to a non-financial foreign entity unless such entity provides the withholding agent with either a certification that it does not have any substantial direct or indirect U.S. owners or provides information regarding substantial direct and indirect U.S. owners of the entity. An intergovernmental agreement between the United States and an applicable foreign country may modify those requirements. The withholding tax described above will not apply if the foreign financial institution or non-financial foreign entity otherwise qualifies for an exemption from the rules.

The withholding provisions described above currently apply to payments of dividends, and, subject to the recently released proposed Treasury Regulations described below, will apply to payments of gross proceeds from a sale or other disposition of common stock on or after January 1, 2019.

The U.S. Treasury Department recently released proposed regulations which, if finalized in their present form, would eliminate the federal withholding tax of 30% applicable to the gross proceeds of a disposition of our common stock. In its preamble to such proposed regulations, the U.S. Treasury Department stated that taxpayers may generally rely on the proposed regulations until final regulations are issued. Holders are encouraged to consult with their own tax advisors regarding the possible implications of FATCA on their investment in our common stock.

EACH PROSPECTIVE INVESTOR SHOULD CONSULT ITS OWN TAX ADVISOR REGARDING THE TAX CONSEQUENCES OF PURCHASING, HOLDING, AND DISPOSING OF OUR COMMON STOCK, INCLUDING THE CONSEQUENCES OF ANY RECENT OR PROPOSED CHANGE IN APPLICABLE LAW.

UNDERWRITING

SVB Leerink LLC, Wells Fargo Securities, LLC and William Blair & Company, L.L.C. are acting as representatives of each of the underwriters named below and as joint book-running managers for this offering. Subject to the terms and conditions set forth in the underwriting agreement among us and the underwriters, we have agreed to sell to the underwriters, and each of the underwriters has agreed, severally and not jointly, to purchase from us, the number of shares of common stock set forth opposite its name below.

Underwriter	Number of Shares
SVB Leerink LLC	6,250,000
Wells Fargo Securities, LLC	3,750,000
William Blair & Company, L.L.C.	2,500,000
Total	12,500,000

Subject to the terms and conditions set forth in the underwriting agreement, the underwriters have agreed, severally and not jointly, to purchase all of the shares sold under the underwriting agreement if any of the shares are purchased. If an underwriter defaults, the underwriting agreement provides that the purchase commitments of the non-defaulting underwriters may be increased or the underwriting agreement may be terminated.

We have agreed to indemnify the underwriters against certain liabilities, including liabilities under the Securities Act, or to contribute to payments the underwriters may be required to make in respect of those liabilities.

The underwriters are offering the shares, subject to prior sale, when, as and if issued to and accepted by them, subject to approval of legal matters by their counsel, including the validity of the shares, and subject to other conditions contained in the underwriting agreement, such as the receipt by the underwriters of officers' certificates and legal opinions. The underwriters reserve the right to withdraw, cancel or modify offers to the public and to reject orders in whole or in part.

Commissions and Discounts

The representatives have advised us that the underwriters propose initially to offer the shares to the public at the public offering price set forth on the cover page of this prospectus supplement and to dealers at that price less a concession not in excess of $0.144 per share. After the initial offering of the shares, the public offering price, concession or any other term of this offering may be changed by the representatives.

The following table shows the public offering price, underwriting discounts and commissions and proceeds before expenses to us. The information assumes either no exercise or full exercise by the underwriters of their option to purchase additional shares of our common stock.

	Per Share	Total	
		Without Option	With Option
Public offering price	$4.00	$ 50,000,000	$57,500,000
Underwriting discounts and commissions	$0.24	$ 3,000,000	$ 3,450,000
Proceeds, before expenses, to us	$3.76	$ 47,000,000	$54,050,000

We estimate expenses payable by us in connection with this offering, other than the underwriting discounts and commissions referred to above, will be approximately $300,000. We have also agreed to reimburse the underwriters up to $10,000 for their FINRA counsel's fees. In accordance with FINRA Rule 5110, this reimbursement is deemed underwriting compensation for this offering.

Option to Purchase Additional Shares

We have granted an option to the underwriters, exercisable for 30 days after the date of this prospectus supplement, to purchase up to 1,875,000 additional shares at the public offering price, less underwriting discounts and commissions. If the underwriters exercise this option, each underwriter will be obligated, subject to the conditions contained in the underwriting agreement, to purchase a number of additional shares proportionate to that underwriter's initial amount reflected in the above table.

No Sales of Similar Securities

We, our executive officers and directors and certain of our other existing security holders have agreed not to sell or transfer any common stock or securities convertible into or exchangeable or exercisable for common stock, for 60 days after the date of this prospectus supplement without first obtaining the written consent of SVB Leerink LLC and Wells Fargo Securities, LLC on behalf of the underwriters. Specifically, we and these other persons have agreed, with certain limited exceptions, not to directly or indirectly:

- offer, sell, contract to sell, pledge or otherwise dispose of, or enter into any transaction which is designed to, or might reasonably be expected to, result in the disposition of (whether by actual disposition or effective economic disposition due to cash settlement or otherwise), any common stock;
- file or participate in the filing of a registration statement related to the common stock;
- establish or increase a put equivalent position or liquidate or decrease a call equivalent position, with respect to any common stock; or
- publicly announce an intention to effect any such transaction.

The lock-up provisions apply to common stock and to securities convertible into or exchangeable or exercisable for common stock. They also apply to common stock owned now or acquired later by the person executing the lock-up agreement or for which the person executing the lock-up agreement later acquires the power of disposition. It does not apply to an aggregate of up to 37,386 shares that may be sold by an executive officer pursuant to a Rule 10b5-1 trading plan in place as of the date of this prospectus supplement.

Nasdaq Global Select Market Listing

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

Price Stabilization, Short Positions and Penalty Bids

Until the distribution of the shares is completed, SEC rules may limit underwriters and selling group members from bidding for and purchasing our common stock. However, the representatives may engage in transactions that stabilize the price of the common stock, such as bids or purchases to peg, fix or maintain that price.

In connection with this offering, the underwriters may purchase and sell our common stock in the open market. These transactions may include short sales, purchases on the open market to cover positions created by short sales and stabilizing transactions. Short sales involve the sale by the underwriters of a greater number of shares than they are required to purchase in this offering. "Covered" short sales are sales made in an amount not greater than the underwriters' option to purchase additional shares described above. The underwriters may close out any covered short position by either exercising their option to purchase additional shares or purchasing shares in the open market. In determining the source of shares to close out the covered short position, the underwriters will consider, among other things, the price of shares available for purchase in the open market as compared to the price at which they may purchase shares through the option to purchase additional shares granted to them under the underwriting agreement described above. "Naked" short sales are sales in excess of such option to

purchase additional shares. The underwriters must close out any naked short position by purchasing shares in the open market. A naked short position is more likely to be created if the underwriters are concerned that there may be downward pressure on the price of our common stock in the open market after pricing that could adversely affect investors who purchase in this offering. Stabilizing transactions consist of various bids for or purchases of shares of common stock made by the underwriters in the open market prior to the closing of this offering.

The underwriters may also impose a penalty bid. This occurs when a particular underwriter repays to the underwriters a portion of the underwriting discount received by it because the representatives have repurchased shares sold by or for the account of such underwriter in stabilizing or short covering transactions.

Similar to other purchase transactions, the underwriters' purchases to cover the syndicate short sales may have the effect of raising or maintaining the market price of our common stock or preventing or retarding a decline in the market price of our common stock. As a result, the price of our common stock may be higher than the price that might otherwise exist in the open market. The underwriters may conduct these transactions on the Nasdaq Global Select Market, in the over-the-counter market or otherwise.

Neither we nor any of the underwriters make any representation or prediction as to the direction or magnitude of any effect that the transactions described above may have on the price of our common stock. In addition, neither we nor any of the underwriters make any representation that the representatives will engage in these transactions or that these transactions, once commenced, will not be discontinued without notice.

The underwriters may also engage in passive market making transactions in our common stock on the Nasdaq Global Select Market in accordance with Rule 103 of Regulation M during a period before the commencement of offers or sales of shares of our common stock in this offering and extending through the completion of distribution. A passive market maker must display its bid at a price not in excess of the highest independent bid of that security. However, if all independent bids are lowered below the passive market maker's bid, that bid must then be lowered when specified purchase limits are exceeded.

Electronic Distribution

In connection with this offering, certain of the underwriters or securities dealers may distribute prospectuses by electronic means, such as e-mail.

Other Relationships

The underwriters and certain of their affiliates are full service financial institutions engaged in various activities, which may include securities trading, commercial and investment banking, financial advisory, investment management, investment research, principal investment, hedging, financing and brokerage activities. Some of the underwriters and certain of their affiliates have and may in the future engage in investment banking and other commercial dealings in the ordinary course of business with us and our affiliates, for which they may in the future receive customary fees, commissions and expenses.

In addition, in the ordinary course of their business activities, the underwriters and their affiliates may make or hold a broad array of investments and actively trade debt and equity securities (or related derivative securities) and financial instruments (including bank loans) for their own account and for the accounts of their customers. Such investments and securities activities may involve securities and/or instruments of ours or our affiliates. The underwriters and their affiliates may also make investment recommendations and/or publish or express independent research views in respect of such securities or financial instruments and may hold, or recommend to clients that they acquire, long and/or short positions in such securities and instruments.

Selling Restrictions

Notice to Prospective Investors in the European Economic Area

In relation to each Member State of the European Economic Area which has implemented the Prospectus Directive (each, a "Relevant Member State"), with effect from and including the date on which the Prospectus Directive is implemented in that Relevant Member State, no offer of shares may be made to the public in that Relevant Member State other than:

A. to any legal entity which is a qualified investor as defined in the Prospectus Directive;

B. to fewer than 150 natural or legal persons (other than qualified investors as defined in the Prospectus Directive), as permitted under the Prospectus Directive, subject to obtaining the prior consent of the representatives; or

C. in any other circumstances falling within Article 3(2) of the Prospectus Directive,

provided that no such offer of shares shall require the Company or the representatives to publish a prospectus pursuant to Article 3 of the Prospectus Directive or supplement a prospectus pursuant to Article 16 of the Prospectus Directive.

Each person in a Relevant Member State who initially acquires any shares or to whom any offer is made will be deemed to have represented, acknowledged and agreed that it is a "qualified investor" within the meaning of the law in that Relevant Member State implementing Article 2(1)(e) of the Prospectus Directive. In the case of any shares being offered to a financial intermediary as that term is used in Article 3(2) of the Prospectus Directive, each such financial intermediary will be deemed to have represented, acknowledged and agreed that the shares acquired by it in the offer have not been acquired on a non-discretionary basis on behalf of, nor have they been acquired with a view to their offer or resale to, persons in circumstances which may give rise to an offer of any shares to the public other than their offer or resale in a Relevant Member State to qualified investors as so defined or in circumstances in which the prior consent of the representatives has been obtained to each such proposed offer or resale.

We, the representatives and each of our and the representatives' affiliates will rely upon the truth and accuracy of the foregoing representations, acknowledgements and agreements.

This prospectus supplement has been prepared on the basis that any offer of shares in any Relevant Member State will be made pursuant to an exemption under the Prospectus Directive from the requirement to publish a prospectus for offers of shares. Accordingly, any person making or intending to make an offer in that Relevant Member State of shares which are the subject of the offering contemplated in this prospectus supplement may only do so in circumstances in which no obligation arises for the company or any of the underwriters to publish a prospectus pursuant to Article 3 of the Prospectus Directive in relation to such offer. Neither we nor the underwriters have authorized, nor do they authorize, the making of any offer of shares in circumstances in which an obligation arises for the company or the underwriters to publish a prospectus for such offer.

For the purpose of the above provisions, the expression "an offer to the public" in relation to any shares in any Relevant Member State means the communication in any form and by any means of sufficient information on the terms of the offer and the shares to be offered so as to enable an investor to decide to purchase or subscribe the shares, as the same may be varied in the Relevant Member State by any measure implementing the Prospectus Directive in the Relevant Member State and the expression "Prospectus Directive" means Directive 2003/71/EC (including the 2010 PD Amending Directive, to the extent implemented in the Relevant Member States) and includes any relevant implementing measure in the Relevant Member State and the expression "2010 PD Amending Directive" means Directive 2010/73/EU.

MiFID II Product Governance

Any person offering, selling or recommending the shares (a "distributor") should take into consideration the manufacturers' target market assessment; however, a distributor subject to MiFID II is responsible for undertaking its own target market assessment in respect of the shares (by either adopting or refining the manufacturers' target market assessment) and determining appropriate distribution channels.

Notice to Prospective Investors in the United Kingdom

In addition, in the United Kingdom, this document is being distributed only to, and is directed only at, and any offer subsequently made may only be directed at persons who are "qualified investors" (as defined in the Prospectus Directive) (i) who have professional experience in matters relating to investments falling within Article 19(5) of the Financial Services and Markets Act 2000 (Financial Promotion) Order 2005, as amended (the "Order") and/or (ii) who are high net worth companies (or persons to whom it may otherwise be lawfully communicated) falling within Article 49(2)(a) to (d) of the Order (all such persons together being referred to as "relevant persons") or otherwise in circumstances which have not resulted and will not result in an offer to the public of the shares in the United Kingdom within the meaning of the Financial Services and Markets Act 2000.

Any person in the United Kingdom that is not a relevant person should not act or rely on the information included in this document or use it as basis for taking any action. In the United Kingdom, any investment or investment activity that this document relates to may be made or taken exclusively by relevant persons.

Notice to Prospective Investors in Canada

The shares may be sold only to purchasers purchasing, or deemed to be purchasing, as principal that are accredited investors, as defined in National Instrument 45-106 Prospectus Exemptions or subsection 73.3(1) of the Securities Act (Ontario), and are permitted clients, as defined in National Instrument 31-103 Registration Requirements, Exemptions and Ongoing Registrant Obligations. Any resale of the shares must be made in accordance with an exemption from, or in a transaction not subject to, the prospectus requirements of applicable securities laws.

Securities legislation in certain provinces or territories of Canada may provide a purchaser with remedies for rescission or damages if this prospectus supplement (including any amendment thereto) contains a misrepresentation, provided that the remedies for rescission or damages are exercised by the purchaser within the time limit prescribed by the securities legislation of the purchaser's province or territory. The purchaser should refer to any applicable provisions of the securities legislation of the purchaser's province or territory for particulars of these rights or consult with a legal advisor.

Pursuant to section 3A.3 of National Instrument 33-105 Underwriting Conflicts (NI 33-105), the underwriters are not required to comply with the disclosure requirements of NI 33-105 regarding underwriter conflicts of interest in connection with this offering.

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, GC&H Investments and GC&H Investments, LLC, entities comprised of partners and associates of Cooley LLP, beneficially own an aggregate of 2,378 shares of our common stock. Mintz, Levin, Cohn, Ferris, Glovsky and Popeo, P.C., Boston, Massachusetts, is representing the underwriters in connection with the 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 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 MORE 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 supplement 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. 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 supplement 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;
- 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 (Item 8.01), January 14, 2019 and June 3, 2019; and
- the description of our common stock in our registration statement on Form 8-A, filed with the SEC on September 25, 2014, including any amendments or reports filed for the purposes of updating such description.

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. 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

Exhibits to the filings will not be sent, however, unless those exhibits have specifically been incorporated by reference in this prospectus supplement and the accompanying prospectus.

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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.

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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 66⅔% 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

12,500,000 Shares

Common Stock

PROSPECTUS SUPPLEMENT

Joint Book-Running Managers

SVB Leerink **Wells Fargo Securities** **William Blair**

June 18, 2019