

Calithera Biosciences, Inc.
Form 424B5
November 24, 2015
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Filed Pursuant to Rule 424(b)(5)
Registration No. 333-207905

PROSPECTUS

\$50,000,000

Common Stock

We have entered into a Sales Agreement, or the Sales Agreement, with Cowen and Company, LLC, dated November 9, 2015, relating to shares of our common stock, par value \$0.0001 per share, offered by this prospectus. In accordance with the terms of the sales agreement, we may offer and sell shares of our common stock having an aggregate offering price of up to \$50,000,000 from time to time through Cowen and Company, LLC, acting as agent.

Under the terms of the Sales Agreement, if we sell shares of our common stock to Cowen and Company, LLC as principal, we will enter into a separate terms agreement with Cowen and Company, LLC. Sales of our common stock, if any, under this prospectus and the accompanying prospectus may be made in sales deemed to be at-the-market equity offerings as defined in Rule 415 promulgated under the Securities Act of 1933, as amended, or the Securities Act. Subject to the terms of the Sales Agreement, we agreed to issue and sell exclusively through Cowen and Company, LLC acting as sales agent or directly to Cowen and Company, LLC acting as principal from time to time, and Cowen and Company, LLC agreed to use its commercially reasonable efforts to sell on our behalf the shares of our common stock offered by this prospectus. Sales of our common stock, if any, through Cowen and Company, LLC acting as sales agent or directly to Cowen and Company, LLC acting as principal will be made by means of ordinary brokers transactions on the NASDAQ Global Select Market, or otherwise at market prices prevailing at the time of sale or at prices related to such prevailing market prices, or at negotiated prices, or, with our prior approval, in privately negotiated transactions. There is no arrangement for funds to be received in any escrow, trust or similar arrangement.

We will pay Cowen and Company, LLC a commission of up to 3.0% of the gross sales price per share for sales under the Sales Agreement. See Plan of Distribution beginning on page 14 for additional information regarding the compensation to be paid to Cowen. In connection with the sale of our common stock on our behalf, Cowen and Company, LLC may be deemed to be an underwriter within the meaning of the Securities Act and the compensation of Cowen and Company, LLC may be deemed to be underwriting commissions or discounts. We have also agreed to provide indemnification and contribution to Cowen and Company, LLC with respect to certain liabilities, including

liabilities under the Securities Act.

Our common stock is listed on the NASDAQ Global Select Market under the symbol CALA. On November 23, 2015, the last reported sale price of our common stock on the NASDAQ Global Select Market was \$7.23 per share.

Investing in our securities involves a high degree of risk. Before making an investment decision, please read the information under the section titled Risk Factors beginning on page 6 of this prospectus and in the documents incorporated by reference into this prospectus.

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.

Cowen and Company

The date of this prospectus is November 24, 2015

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ABOUT THIS PROSPECTUS

This prospectus is part of a registration statement that we have filed with the Securities and Exchange Commission, or the SEC, utilizing a shelf registration process. Under the shelf registration process, we may offer shares of our common stock having an aggregate offering price of up to \$150,000,000. Under this prospectus, we may offer shares of our common stock having an aggregate offering price of up to \$50,000,000 from time to time at prices and on terms to be determined by market conditions at the time of offering.

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

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

You should rely only on the information contained in, or incorporated by reference into, this prospectus and in any free writing prospectus that we may authorize for use in connection with this offering. We have not, and Cowen and Company, LLC, or Cowen, has not, authorized any other person to provide you with different information. If anyone provides you with different or inconsistent information, you should not rely on it. We and Cowen take no responsibility for, and can provide no assurance as to the reliability of, any other information that others may give

you. We are not, and Cowen is not, making an offer to sell or soliciting an offer to buy our securities in any jurisdiction in which an offer or solicitation is not authorized or in which the person making that offer or solicitation is not qualified to do so or to anyone to whom it is unlawful to make an offer or solicitation. You should assume that the information appearing in this prospectus, the documents incorporated by reference into this prospectus, and in any free writing prospectus that we may authorize for use in connection with this offering, is accurate only as of the date of those respective documents. Our business, financial condition, results of operations and prospects may have changed since those dates.

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

INDUSTRY AND MARKET DATA

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

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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 and any related free writing prospectus, including the risks of investing in our securities discussed under the section titled Risk Factors contained in this prospectus 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 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 drugs directed against tumor metabolism and tumor immunology targets for the treatment of cancer. Tumor metabolism and tumor immunology 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. Our lead product candidate, CB-839, is an internally discovered, first-in-class inhibitor of glutaminase, a critical enzyme in tumor metabolism. We are currently evaluating CB-839 in three Phase 1 clinical trials in solid and hematological tumors. Our first program in tumor immunology, CB-1158, is directed at developing inhibitors of the enzyme arginase and is an orally bioavailable, first-in-class agent for this novel immuno-oncology target and is expected to enter clinical development in the first half of 2016. We also have a preclinical program in tumor metabolism which seeks to develop inhibitors of the enzyme hexokinase II, the first step in the breakdown of glucose, an essential nutrient in many cancer cells. Our ongoing research efforts are focused on discovering additional product candidates against novel tumor metabolism and immunology targets.

Recent Developments

CB-839 is a potent, selective, reversible and orally bioavailable inhibitor of human glutaminase. CB-839 binds to a unique site on glutaminase that is distinct from the site that binds glutamine, thereby reducing the potential for undesirable side effects due to inhibition of other enzymes and receptors that bind glutamine. In our preclinical studies, CB-839 has been shown to halt the growth of or kill cancer cells across a range of tumor types. The compound has demonstrated antitumor activity in several different tumor models in animals. In addition, CB-839 has shown strong synergy with immunomodulatory agents and several kinase inhibitors that target growth factor pathways. In preclinical toxicology studies, CB-839 was well tolerated in animals at doses above those shown to inhibit tumor growth. In December 2013, we submitted an IND application to the FDA to enable the initiation of three Phase 1 trials in patients with both solid and hematological tumors.

In February 2014, we initiated three Phase 1 clinical trials of CB-839 in patients with solid and hematological tumors. CX-839-001 is enrolling patients with solid tumors, CX-839-002 is enrolling patients with multiple myeloma or non-Hodgkin's lymphoma, and CX-839-003 is enrolling patients with acute myeloid or acute lymphocytic leukemia. The objectives of the Phase 1 clinical trials are to assess the safety and tolerability of CB-839. Each trial includes a dose escalation stage to identify the optimal dose for future clinical trials. This dose will be determined by the extent of glutaminase inhibition in blood and tumors, or by identifying a maximum tolerated dose. Each trial will also have an expansion stage in which additional patients with specific tumor types will be enrolled to further evaluate the safety of CB-839 and to seek preliminary evidence of efficacy. In addition to evaluating CB-839 as a single agent, we plan to enroll six Phase 1b combination cohorts, one in which CB-839 will be combined with paclitaxel in patients with

triple-negative breast cancer, a second in

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which CB-839 will be combined with everolimus in renal cell cancer, a third in which CB-839 will be combined with erlotinib in non-small cell lung cancer, a fourth in which CB-839 will be combined with dexamethasone in patients with multiple myeloma, a fifth in which CB-839 will be combined with pomalidomide (marketed as Pomalyst) and dexamethasone in patients with multiple myeloma, and a sixth in which CB-839 will be combined with azacitadine in acute myelogenous leukemia. The goal of these cohorts is to evaluate the safety and potential utility of CB-839 when used in combination with these drugs. We expect hematologic Phase 1 clinical trial data by year-end 2015 and initial data from our combination trials to be available in 2016.

On November 8, 2015, solid tumor phase 1 data were presented at the American Association of Cancer Research-National Cancer Institute-European Organization for Research and Treatment of Cancer meeting in Boston, Massachusetts that demonstrated the clinical activity, tolerability and unique mechanism of action of CB-839 as a single agent in patients with solid tumors. Among efficacy-evaluable patients across a range of tumor types treated on the twice daily schedule of CB-839 administered with food, 22 of 50 patients (44%) had stable disease, or SD, or better lasting at least 3 cycles (63 days). Five stable disease patients currently on study have been treated with CB-839 for over 8 months without progression. This includes 2 patients with triple negative breast cancer, 1 renal cell carcinoma patient, 1 mesothelioma patient and 1 IDH1 mutant chondrosarcoma patient. In renal cell carcinoma, one patient has an ongoing partial response (PR; on study >5 months); this patient showed a 32% reduction in target lesions by RECIST with generalized shrinkage of lymph node metastases. Among the 15 evaluable patients with renal cell carcinoma, 9 (60%) had SD or PR, with four patients remaining on study.

We are currently evaluating a combination of CB-839 with the mTOR (mammalian target of rapamycin) inhibitor everolimus in the CX-839-001 Phase 1 study and additional combinations are anticipated in the near future with other approved agents, as described above. Data we presented at the American Association of Cancer Research in April 2015 demonstrated that signaling through mTOR is down-regulated by CB-839, highlighting a relationship between signal transduction pathways and cancer metabolism. This relationship is supported by data showing that CB-839 synergizes with everolimus in renal cell carcinoma lines. In addition, we showed that CB-839 has synergistic activity with the tyrosine kinase inhibitors sunitinib, sorafenib, and pazopanib, all of which are approved for the treatment of renal cell carcinoma.

We selected CB-1158 as our lead clinical candidate for our first immuno-oncology program targeting inhibition of arginase, a critical T-cell immunosuppressive enzyme produced by myeloid-derived suppressor cells in tumors. In November 2015, we presented data at the American Association of Cancer Research-National Cancer Institute-European Organization for Research and Treatment of Cancer meeting showing that CB-1158 is a highly selective, orally bioavailable, small molecule inhibitor of human arginase with nanomolar potency. Administration of CB-1158 to mice results in a dose-dependent increase in tumor arginine levels up to ~4-fold, consistent with target inhibition. Evaluation of anti-tumor efficacy in immunocompetent syngeneic mouse studies has shown that CB-1158 administered twice daily for 2-4 weeks results in significant inhibition of tumor growth. CB-1158 combines well with checkpoint inhibitors in syngeneic tumor studies, providing additional reduction in tumor growth and an increase in the CD8⁺ T-cell population in tumors with no evidence of additional toxicity. The compound has low clearance in mice, rats, dogs, and monkeys. Low clearance is predicted for CB-1158 in humans based on excellent stability in animal and human liver cells. Preclinical in vitro and in vivo data predict good oral bioavailability of CB-1158 in humans. Twice daily oral administration of CB-1158 to rats at 450 mg/kg (900 mg/kg/day) for 14 days resulted in no severe toxicity. We anticipate filing an investigational new drug application for CB-1158 in the first half of 2016.

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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 \$76.4 million as of September 30, 2015.

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.

Clinical trials of our product candidates will be costly and time consuming, and if they fail to demonstrate safety and efficacy to the satisfaction of the FDA, or similar regulatory authorities, we will be unable to commercialize our product candidates.

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.

If we are unable to obtain sufficient intellectual property protection or protect our intellectual property rights, our business may be harmed.

Healthcare policy and regulatory oversight in the United States and internationally are subject to rapid change, and if we are unable to respond, our business may be harmed.

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 intend to 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 this prospectus, 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 for up to five years 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

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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.

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The Offering

Common stock offered by us	Shares of our common stock, par value \$0.0001 per share, with an aggregate sale price of up to \$50,000,000.
Common stock to be outstanding after this offering	Up to 25,050,656 shares, assuming the sale of 6,915,629 shares of our common stock in this offering at a public offering price of \$7.23 per share, which was the last reported sale price of our common stock on the NASDAQ Global Select Market on November 23, 2015. The actual number of shares issued will vary depending on the sales price under this offering.
Manner of offering	At-the-market offering that may be made from time to time through or to Cowen, as sales agent and/or principal. See Plan of Distribution on page 14.
Use of Proceeds	We intend to use the net proceeds from this offering, if any, to fund our clinical trials and for working capital and general corporate purposes. See Use of Proceeds on page 7.
Risk Factors	Investment in our securities involves a high degree of risk. You should read the Risk Factors, beginning on page 5 of this prospectus and in the documents incorporated by reference into this prospectus for a discussion of factors to consider before deciding to purchase shares of our common stock.

NASDAQ Global Select Market Symbol: CALA

The number of our shares of common stock outstanding after this offering is based on 18,135,027 shares of common stock outstanding as of September 30, 2015, and excludes:

1,729,706 shares of common stock issuable upon the exercise of options outstanding as of September 30, 2015 with a weighted-average exercise price of \$8.54 per share;

969,076 shares of common stock reserved for future issuance under our 2014 Equity Incentive Plan, as well as any automatic increases in the number of shares of common stock reserved for future issuance under this plan; and

337,027 shares reserved for future issuance under our 2014 Employee Stock Purchase Plan, as well as any automatic increases in the number of shares of common stock reserved for future issuance under this plan.

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RISK FACTORS

You should consider carefully the risks described below and discussed under the section titled Risk Factors contained in our annual report on Form 10-K for the year ended December 31, 2014, and in our subsequent quarterly reports on Form 10-Q as updated by our subsequent filings under the Securities Exchange Act of 1934, as amended, or the Exchange Act, each of which is incorporated by reference in this prospectus in their entirety, together with other information in this prospectus, and the information and documents incorporated by reference in this prospectus, and any free writing prospectus that we have authorized for use in connection with this offering before you make a decision to invest in our common stock. If any of the following events actually occur, our business, financial condition, results of operations or cash flow could be harmed. This could cause the trading price of our common stock to decline and you may lose all or part of your investment. The risks below and incorporated by reference in this prospectus are not the only ones we face. Additional risks not currently known to us or that we currently deem immaterial may also affect our business operations. Please also read carefully the section below titled Special Note Regarding Forward-Looking Statements.

Additional Risks Relating To The Offering

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

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

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

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

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

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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 expectations with respect to the clinical development of our product candidates, our clinical trials and the regulatory approval process;

statements regarding the steps, timing and costs of our development programs;

any projections of earnings, revenue, sufficiency of cash resources or other financial items;

the plans and objectives of management for future operations;

the availability of additional financing and access to capital;

the formation of a trading market for our common stock;

discussions and approvals of regulatory agencies; and

the period of time for which we will be able to fund our operations.

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, sho of these terms or other similar expressions. These statements reflect our current views with respect to future events and are based on assumptions and are subject to risks and uncertainties. Given these uncertainties, you should not place undue reliance on these forward-looking statements. We discuss in greater detail many of these risks under the

section titled "Risk Factors" contained in this prospectus, 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 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.

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USE OF PROCEEDS

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

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

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

Our net tangible book value as of September 30, 2015, was \$78.6 million, or \$4.33 per share. Net tangible book value is total tangible assets less our total liabilities divided by the number of outstanding shares of common stock.

After giving effect to the sale of \$50,000,000 of shares common stock in this offering at an assumed public offering price of \$7.23 per share, which was the closing price of our common stock as reported on NASDAQ Global Select Market on November 23, 2015, and after deducting offering commissions and expenses payable by us, our net tangible book value as of September 30, 2015, would have been \$126.9 million, or \$5.07 per share of common stock. This represents an immediate increase in net tangible book value of \$0.73 per share to our existing stockholders and an immediate dilution in net tangible book value of \$2.16 per share to investors participating in this offering. The following table illustrates this dilution per share to investors participating in this offering:

Assumed public offering price per share	\$ 7.23
Net tangible book value per share as of September 30, 2015	\$ 4.33
Increase in net tangible book value per share attributable to new investors in offering	\$ 0.73
As adjusted net tangible book value per share after this offering	5.07
Dilution per share to new investors	\$ 2.16

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

The above discussion and table are based on shares of our common stock issued and outstanding after this offering as of September 30, 2015, and excludes:

1,729,706 shares issuable upon the exercise of options outstanding at a weighted-average exercise price of \$8.54 per share;

969,076 shares of common stock reserved for future issuance under our 2014 Equity Incentive Plan, as well as automatic increases in the number of shares of common stock reserved for future issuances under this plan; and

337,027 shares of common stock reserved for future issuance under our 2014 Employee Stock Purchase Plan, as well as automatic increases in the number of shares of common stock reserved for future issuances under this plan.

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

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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.

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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.

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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 66 ²/₃% 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;

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provide that our board of directors will be classified into three classes of directors;

provide that, subject to the rights of any series of preferred stock to elect directors, directors may only be removed for cause, which removal may be effected, subject to any limitation imposed by law, by the holders of at least a majority of the voting power of all of our then-outstanding shares of the capital stock entitled to vote generally at an election of directors;

provide that all vacancies, including newly created directorships, may, except as otherwise required by law, be filled by the affirmative vote of a majority of directors then in office, even if less than a quorum;

require that any action to be taken by our stockholders must be effected at a duly called annual or special meeting of stockholders and not be taken by written consent or electronic transmission;

provide that stockholders seeking to present proposals before a meeting of stockholders or to nominate candidates for election as directors at a meeting of stockholders must provide advance notice in writing, and also specify requirements as to the form and content of a stockholder's notice;

provide that special meetings of our stockholders may be called only by the chairman of our board of directors, our chief executive officer or by our board of directors pursuant to a resolution adopted by a majority of the total number of authorized directors; and

not provide for cumulative voting rights, therefore allowing the holders of a majority of the shares of common stock entitled to vote in any election of directors to elect all of the directors standing for election, if they should so choose.

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

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

These provisions are intended to enhance the likelihood of continued stability in the composition of our board of directors and its policies and to discourage coercive takeover practices and inadequate takeover bids. These provisions are also designed to reduce our vulnerability to hostile takeovers and to discourage certain tactics that may be used in proxy fights. However, such provisions could have the effect of discouraging others from making tender offers for our shares and may have the effect of delaying changes in our control or management. As a consequence, these provisions may also inhibit fluctuations in the market price of our stock that could result from actual or rumored takeover attempts. We believe that the benefits of these provisions, including increased protection of our potential ability to

negotiate with the proponent of an unfriendly or unsolicited proposal to acquire or restructure our company, outweigh the disadvantages of discouraging takeover proposals, because negotiation of takeover proposals could result in an improvement of their terms.

Choice of Forum

Our amended and restated certificate of incorporation provides that the Court of Chancery of the State of Delaware will be the exclusive forum for any derivative action or proceeding brought on our behalf; any action asserting a breach of fiduciary duty; any action asserting a claim against us arising pursuant to the Delaware General Corporation Law, our certificate of incorporation or our bylaws; or any action asserting a claim against us that is governed by the internal affairs doctrine. The enforceability of similar choice of forum provisions in

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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 1st Avenue, Brooklyn, New York 11219.

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PLAN OF DISTRIBUTION

We have entered into the Sales Agreement with Cowen, under which we may issue and sell from time to time up to \$50,000,000 of our common stock through Cowen as our sales agent. Sales of our common stock, if any, will be made at market prices by any method that is deemed to be an at the market offering as defined in Rule 415 under the Securities Act, including sales made directly on The Nasdaq Global Select Market or any other trading market for our common stock, or sales to or through a market maker other than on an exchange. If authorized by us in writing, Cowen may also sell our shares of common stock by any other method permitted by law, including negotiated transactions, and Cowen may also purchase shares of our common stock as principal.

Cowen will offer our common stock subject to the terms and conditions of the Sales Agreement on a daily basis or as otherwise agreed upon by us and Cowen. We will designate the maximum amount of common stock to be sold through Cowen on a daily basis or otherwise determine such maximum amount together with Cowen. Subject to the terms and conditions of the Sales Agreement, Cowen will use its commercially reasonable efforts to sell on our behalf all of the shares of common stock requested to be sold by us. We may instruct Cowen not to sell common stock if the sales cannot be effected at or above the price designated by us in any such instruction. Cowen or we may suspend the offering of our common stock being made through Cowen under the Sales Agreement upon proper notice to the other party. Cowen and we each have the right, by giving written notice as specified in the Sales Agreement, to terminate the Sales Agreement in each party's sole discretion at any time.

The aggregate compensation payable to Cowen as sales agent equals up to 3.0% of the gross sales price of the shares sold through it pursuant to the Sales Agreement. We have also agreed to reimburse Cowen up to \$50,000 of Cowen's actual outside legal expenses incurred by Cowen in connection with this offering. We have also agreed to reimburse Cowen for its FINRA counsel fees in an amount up to \$10,000. We estimate that the total expenses of the offering payable by us, excluding commissions payable to Cowen under the Sales Agreement, will be approximately \$300,000.

The remaining sales proceeds, after deducting any expenses payable by us and any transaction fees imposed by any governmental, regulatory, or self-regulatory organization in connection with the sales, will equal our net proceeds for the sale of such common stock.

Cowen will provide written confirmation to us following the close of trading on The Nasdaq Global Select Market on each day in which common stock is sold through it as sales agent under the Sales Agreement. Each confirmation will include the number of shares of common stock sold through it as sales agent on that day, the volume weighted average price of the shares sold, the percentage of the daily trading volume and the net proceeds to us.

We will report at least quarterly the number of shares of common stock sold through Cowen under the Sales Agreement, the net proceeds to us and the compensation paid by us to Cowen in connection with the sales of common stock.

Settlement for sales of common stock will occur, unless the parties agree otherwise, on the third business day that is also a trading day following the date on which any sales were made in return for payment of the net proceeds to us. There is no arrangement for funds to be received in an escrow, trust or similar arrangement.

In connection with the sales of our common stock on our behalf, Cowen may be deemed to be an underwriter within the meaning of the Securities Act, and the compensation paid to Cowen may be deemed to be underwriting commissions or discounts. We have agreed in the Sales Agreement to provide indemnification and contribution to Cowen against certain liabilities, including liabilities under the Securities Act. As sales agent, Cowen will not engage in any transactions that stabilizes our common stock.

Our common stock is listed on The NASDAQ Global Select Market and trades under the symbol CALA. The transfer agent of our common stock is American Stock Transfer & Trust Company, LLC.

Cowen and/or its affiliates have provided, and may in the future provide, various investment banking and other financial services for us for which services they have received and, may in the future receive, customary fees.

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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 8,917 shares of our common stock. Cowen and Company, LLC is being represented by Mintz, Levin, Cohn, Ferris, Glovsky and Popeo, P.C., Boston, Massachusetts in connection with this offering.

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, 2014, 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, 2014, filed with the SEC on March 27, 2015;

Amendment No. 1 to our Annual Report on Form 10-K/A for the year ended December 31, 2014, filed with the SEC on November 12, 2015;

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our Quarterly Report on Form 10-Q for the quarter ended March 31, 2015, filed with the SEC on May 11, 2015.

our Quarterly Report on Form 10-Q for the quarter ended June 30, 2015, filed with the SEC on August 10, 2015.

our Quarterly Report on Form 10-Q for the quarter ended September 30, 2015, filed with the SEC on November 9, 2015.

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the information specifically incorporated by reference in our Annual Report on Form 10-K for the year ended December 31, 2014, from our definitive proxy statement relating to our 2015 annual meeting of stockholders, filed with the SEC on April 24, 2015;

our Current Reports on Form 8-K filed with the SEC on February 11, 2015, March 5, 2015, March 24, 2015, June 10, 2015 and September 30, 2015; and

the description of our common stock in our registration statement on Form 8-A filed with the SEC on September 25, 2014.

We also incorporate by reference any future filings (other than current reports furnished under Item 2.02 or Item 7.01 of Form 8-K and exhibits filed on such form that are related to such items unless such Form 8-K expressly provides to the contrary) made with the SEC pursuant to Sections 13(a), 13(c), 14 or 15(d) of the Exchange Act, including those made after the date of the initial filing of the registration statement of which this prospectus 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

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\$50,000,000

Common Stock

PROSPECTUS

Cowen and Company

November 24, 2015