

EXELIXIS, INC.
 Form 424B7
 February 21, 2014
Table of Contents

Filed Pursuant to Rule 424(b)(7)
 Registration No. 333-194074

CALCULATION OF REGISTRATION FEE

Title of each class of securities to be Registered	Amount to be registered	Proposed maximum aggregate price per unit(1)	Proposed maximum aggregate offering price	Amount of registration fee
Common Stock, par value \$0.001 per share	1,000,000(2)	\$7.1163	\$7,116,300	\$917(3)

- (1) Estimated solely for the purpose of computing the amount of the registration fee pursuant to Rule 457(c) under the Securities Act of 1933, as amended (the **Securities Act**), based on the average of the reported high and low prices of the Common Stock on the NASDAQ Global Select Market on February 20, 2014.
- (2) Pursuant to Rule 416 under the Securities Act, the shares of Common Stock being registered hereunder include such indeterminate number of shares of Common Stock as may be issuable with respect to the shares of Common Stock being registered hereunder as a result of stock splits, stock dividends or similar transactions.
- (3) Calculated pursuant to Section 6(b) of the Securities Act by multiplying the proposed maximum aggregate offering price for the secondary offering by 0.0001288.

Table of Contents

Prospectus Supplement to Prospectus dated February 21, 2014.

1,000,000 Shares

Common Stock

This prospectus supplement relates to the resale of up to 1,000,000 shares of our common stock that we may issue to the selling stockholders named in this prospectus supplement upon the exercise of warrants owned by the selling stockholders. The selling stockholders identified in this prospectus supplement, or their permitted transferees or other successors-in-interest that may be identified in a prospectus supplement, may sell shares from time to time on or off the NASDAQ Global Select Market in regular brokerage transactions, in transactions directly with market makers or in privately negotiated transactions, on a continuous or delayed basis. For additional information on the methods of sale that may be used by the selling stockholders, see the section entitled **Plan of Distribution** on page S-28. We will not receive any of the proceeds from the sale of these shares.

Our common stock is traded on the NASDAQ Global Select Market under the symbol **EXEL**. You should read both this prospectus, and the additional information described under the heading **Incorporation of Certain Documents by Reference**, before you decide to invest in shares of our common stock.

Investing in our common stock involves a high degree of risk. See Risk Factors beginning on page S-3 of this prospectus supplement, and under similar headings in the other documents that are incorporated by reference into this prospectus supplement and the accompanying prospectus or are filed after the date hereof, to read about factors you should consider before purchasing our shares of our common stock.

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

The date of this Prospectus Supplement is February 21, 2014

Table of Contents

Table of Contents
Prospectus Supplement

	Page
<u>ABOUT THIS PROSPECTUS SUPPLEMENT</u>	S-ii
<u>PROSPECTUS SUPPLEMENT SUMMARY</u>	S-1
<u>RISK FACTORS</u>	S-3
<u>SPECIAL NOTE REGARDING FORWARD-LOOKING STATEMENTS</u>	S-26
<u>PRICE RANGE OF OUR COMMON STOCK</u>	S-27
<u>DIVIDEND POLICY</u>	S-27
<u>SELLING STOCKHOLDERS</u>	S-27
<u>USE OF PROCEEDS</u>	S-27
<u>PLAN OF DISTRIBUTION</u>	S-28
<u>VALIDITY OF COMMON STOCK</u>	S-30
<u>EXPERTS</u>	S-30

Prospectus

	Page
<u>ABOUT THIS PROSPECTUS</u>	i
<u>PROSPECTUS SUMMARY</u>	1
<u>RISK FACTORS</u>	2
<u>SPECIAL NOTE REGARDING FORWARD-LOOKING STATEMENTS</u>	2
<u>USE OF PROCEEDS</u>	3
<u>DESCRIPTION OF CAPITAL STOCK</u>	3
<u>SELLING STOCKHOLDERS</u>	5
<u>PLAN OF DISTRIBUTION</u>	5
<u>LEGAL MATTERS</u>	5
<u>EXPERTS</u>	6
<u>WHERE YOU CAN FIND MORE INFORMATION</u>	6
<u>INCORPORATION OF CERTAIN INFORMATION BY REFERENCE</u>	6

Table of Contents

ABOUT THIS PROSPECTUS SUPPLEMENT

This document is in two parts. The first part is this prospectus supplement, which describes the specific terms of the common stock the selling stockholders are offering. The second part, the accompanying prospectus dated February 21, 2014, gives more general information about our common stock. You should read this prospectus supplement and the accompanying prospectus, including the information incorporated by reference and any free writing prospectuses we have authorized for use in connection with this offering, in their entirety before making an investment decision.

You should rely only on the information contained or incorporated by reference in this prospectus supplement and the accompanying prospectus, along with the information contained in any free writing prospectuses we have authorized for use in connection with this offering. If the description of the offering varies between this prospectus supplement and the accompanying prospectus, you should rely on the information in this prospectus supplement. We have not authorized anyone to provide you with different or additional information. Under no circumstances should the delivery to you of this prospectus supplement and the accompanying prospectus or any sale made pursuant to this prospectus supplement create any implication that the information contained in this prospectus supplement or the accompanying prospectus is correct as of any time after the respective dates of such information.

Unless the context requires otherwise, the words Exelixis, we, the company, us and our refer to Exelixis, Inc. and its subsidiaries, and the term you refers to a prospective investor.

This prospectus supplement and the accompanying prospectus, including the information incorporated by reference into this prospectus supplement and the accompanying prospectus, include trademarks, service marks and trade names owned by us or others. Exelixis, Inc., the Exelixis, Inc. logo and all other Exelixis product and service names are trademarks of Exelixis, Inc. in the United States and in other selected countries. All other trademarks, service marks and trade names included or incorporated by reference in this prospectus supplement and the accompanying prospectus are the property of their respective owners.

Table of Contents

PROSPECTUS SUPPLEMENT SUMMARY

*This summary highlights selected information appearing elsewhere or incorporated by reference in this prospectus supplement and accompanying prospectus and any free writing prospectus that we have authorized for use in connection with this offering and may not contain all of the information that is important to you. This prospectus supplement and the accompanying prospectus include information about the shares the selling stockholders are offering as well as information regarding our business and financial data. You should read this prospectus supplement and the accompanying prospectus, including the information incorporated by reference and any free writing prospectuses we have authorized for use in connection with this offering, in their entirety. Investors should carefully consider the information set forth under *Risk Factors* in this prospectus supplement.*

Exelixis, Inc.

We are a biotechnology company committed to developing small molecule therapies for the treatment of cancer. Our two most advanced assets, COMETRIQ® (cabozantinib), our wholly-owned inhibitor of multiple receptor tyrosine kinases, and cobimetinib (GDC-0973/XL518), a potent, highly selective inhibitor of MEK, which we out-licensed to Genentech, Inc. (a wholly-owned member of the Roche Group), or Genentech, are currently the subject of six ongoing phase 3 pivotal trials. Top-line results from four of these pivotal trials are expected in 2014.

Corporate Information

We were incorporated in Delaware in November 1994 as Exelixis Pharmaceuticals, Inc. and we changed our name to Exelixis, Inc. in February 2000. Our principal executive offices are located at 210 East Grand Ave., South San Francisco, California 94080. Our telephone number is (650) 837-7000 and our website is <http://www.exelixis.com>. We have not incorporated by reference into this prospectus supplement or the accompanying prospectus the information on our website, and you should not consider it to be a part of this prospectus supplement. Our website address is included in this prospectus supplement as an inactive textual reference only.

Our Fiscal Year

We have adopted a 52- or 53-week fiscal year that generally ends on the Friday closest to December 31st. Fiscal year 2011, a 52-week year, ended on December 30, 2011, fiscal year 2012, a 52-week year, ended on December 28, 2012, fiscal year 2013, a 52-week year, ended on December 27, 2013, and fiscal year 2014, a 53-week year, will end on January 2, 2015. For convenience, references in this prospectus supplement as of and for the fiscal years ended December 30, 2011, December 28, 2012 and December 27, 2013, are indicated on a calendar year basis, ended December 31, 2011, 2012 and 2013, respectively.

Table of Contents

The Offering

Common stock offered by the selling stockholders	1,000,000 shares
Common stock to be outstanding after the offering	195,533,651 shares
Use of proceeds	We will not receive any proceeds from the sale of the shares being sold by the selling stockholders.
Risk factors	See Risk Factors beginning on page S-3 for a discussion of factors you should consider before buying shares of our common stock.

NASDAQ Global Select Market Symbol **EXEL**

The number of shares of common stock to be outstanding after the offering is based on the number of shares outstanding as of December 31, 2013, which as of that date was 184,533,651 shares, and also includes the 10,000,000 shares of our common stock we issued in our underwritten public offering in January 2014 and 1,000,000 shares of common stock underlying the warrants issued to the selling stockholders in January 2014, but excludes:

23,983,275 shares of common stock underlying options outstanding as of December 31, 2013, at a weighted average exercise price of \$6.48 per share;

1,441,215 shares of common stock underlying warrants outstanding as of December 31, 2013, at a weighted average exercise price of \$6.99 per share;

1,810,521 shares reserved for future issuance pursuant to unvested restricted stock units as of December 31, 2013;

1,709,233 shares available for future grant under our 2011 Equity Incentive Plan, 2,040,839 shares available for future purchase under our 2000 Employee Stock Purchase Plan, no shares available for future grant under our 2000 Non-Employee Directors Stock Option Plan, and 857,396 shares available for future grant under our 401(k) Retirement Plan, all as of December 31; and

54,117,649 shares of common stock reserved for issuance upon conversion of our outstanding 4.25% convertible senior subordinated notes due 2019, or the 2019 Notes.

Table of Contents

RISK FACTORS

Investing in our common stock involves a high degree of risk. Before deciding whether to invest in our common stock, you should consider carefully the risk factors described below and in any free writing prospectus that we have authorized for use in connection with this offering. If any of these risks actually occur, it may materially harm our business, financial condition, operating results or cash flow. As a result, the market price of our common stock could decline, and you could lose all or part of your investment. Additional risks and uncertainties that are not yet identified or that we think are immaterial may also materially harm our business, operating results and financial condition and could result in a complete loss of your investment.

Risks Related to Our Need for Additional Financing and Our Financial Results

If additional capital is not available to us, we may be forced to delay, reduce or eliminate our product development programs or commercialization efforts and we may breach our financial covenants.

We may need to raise additional capital to:

fund our operations and clinical trials;

continue our research and development efforts; and

commercialize cabozantinib or any other future product candidates, if any such candidates receive regulatory approval for commercial sale; and

fund the U.S. marketing and commercialization costs for cobimetinib (GDC-0973/XL518) we are obligated to share under our collaboration with Genentech or any similar costs we are obligated to fund under collaborations we may enter into in the future.

As of December 31, 2013, we had \$415.9 million in cash and investments, which included short- and long-term restricted cash and investments of \$12.2 million and \$16.9 million, respectively, and short- and long-term unrestricted investments of \$138.5 million and \$144.3 million, respectively. We are required to maintain on deposit with Silicon Valley Bank or one of its affiliates short- and long-term unrestricted investments of \$1.8 million and \$81.9 million, respectively, pursuant to covenants in our loan and security agreement with Silicon Valley Bank. We anticipate that our current cash and cash equivalents, short- and long-term investments and product revenues will enable us to maintain our operations for a period of at least 12 months following the end of 2013. However, our future capital requirements will be substantial, and we may need to raise additional capital in the future. Our capital requirements will depend on many factors, and we may need to use available capital resources and raise additional capital significantly earlier than we currently anticipate. These factors include:

the progress and scope of the development and commercialization activities with respect to COMETRIQ® (cabozantinib);

repayment of our \$287.5 million aggregate principal amount of the 4.25% convertible senior subordinated notes due 2019, or the 2019 Notes, that mature on August 15, 2019, unless earlier converted, redeemed or repurchased;

repayment of the \$104.0 million principal amount outstanding as of the filing date of this prospectus supplement (\$114.0 million principal amount was outstanding at December 31, 2013) of our secured convertible notes, or the Deerfield Notes, issued to entities affiliated with Deerfield Management Company, L.P., or Deerfield, for which will be required to make a mandatory prepayment on the Deerfield Notes in 2015 equal to 15% of certain revenues from collaborative arrangements (other than intercompany arrangements) received during the prior fiscal year, subject to a maximum prepayment amount of \$27.5 million, and if we exercise our extension option for the Deerfield Notes, for which we may be subject to similar mandatory prepayment obligations in 2016, 2017 and 2018, in each case unless we are able to repay the Deerfield Notes with our common stock, which we are only able to do under specified conditions

Table of Contents

repayment of our term loan and line of credit from Silicon Valley Bank, which had an outstanding balance at December 31, 2013, of \$82.1 million;

the commercial success of COMETRIQ and the revenues we generate;

the level of payments received under existing collaboration agreements, licensing agreements and other arrangements;

the degree to which we conduct funded development activity on behalf of partners to whom we have out-licensed compounds or programs;

whether we enter into new collaboration agreements, licensing agreements or other arrangements (including, in particular, with respect to COMETRIQ (cabozantinib)) that provide additional capital;

our ability to control costs;

our ability to remain in compliance with, or amend or cause to be waived, financial covenants contained in agreements with third parties;

the amount of our cash and cash equivalents, short- and long-term investments that serve as collateral for bank lines of credit;

future clinical trial results;

our need to expand our product and clinical development efforts;

the cost and timing of regulatory approvals;

the cost of clinical and research supplies of our product candidates;

our obligation to share U.S. marketing and commercialization costs for cobimetinib under our collaboration with Genentech;

our ability to share the costs of our clinical development efforts with third parties;

the effect of competing technological and market developments;

the filing, maintenance, prosecution, defense and enforcement of patent claims and other intellectual property rights; and

the cost of any acquisitions of or investments in businesses, products and technologies.

We may seek to raise funds through the sale of equity or debt securities or through external borrowings. In addition, we may enter into additional strategic partnerships, collaborative arrangements or other strategic transactions. It is unclear whether any such partnership, arrangement or transaction will occur, on satisfactory terms or at all, or what the timing and nature of such a partnership, arrangement or transaction may be. The sale of equity or convertible debt securities in the future may be dilutive to our stockholders, and debt-financing arrangements may require us to pledge certain assets and enter into covenants that would restrict certain business activities or our ability to incur further indebtedness, and may contain other terms that are not favorable to our stockholders or us. If we are unable to obtain adequate funds on reasonable terms, we may be required to curtail operations significantly or obtain funds by entering into financing, supply or collaboration agreements on unattractive terms or we may be required to relinquish rights to technology or product candidates or to grant licenses on terms that are unfavorable to us.

We may need to obtain additional funding in order to stay in compliance with financial covenants contained in our loan and security agreement with Silicon Valley Bank. This agreement contains covenants or events of default requiring us to maintain specified collateral balances. The failure to comply with these covenants could result in an acceleration of the underlying debt obligations. If we are unable to remain in compliance with such covenants or if we are unable to renegotiate such covenants and the lender exercises its remedies under the agreement, we would not be able to operate under our current operating plan.

Table of Contents

We have a history of net losses. We expect to continue to incur net losses, and we may not achieve or maintain profitability.

We have incurred annual net losses since inception through the year ended December 31, 2013, with the exception of the fiscal year ended December 31, 2011. In 2011, we had net income primarily as a result of the acceleration of revenue recognized under our 2008 collaboration agreement with Bristol-Myers Squibb that terminated in October 2011 and under our 2009 discovery collaboration agreement with Sanofi that terminated in December 2011. We anticipate net losses and negative operating cash flow for the foreseeable future. For the year ended December 31, 2013, we had a net loss of \$244.8 million; as of December 31, 2013, we had an accumulated deficit of \$1.5 billion. We commercially launched COMETRIQ for the treatment of progressive, metastatic MTC in the United States in late January 2013. From the commercial launch through December 31, 2013, we have generated \$15.0 million in net revenues from the sale of COMETRIQ. We have derived substantially all of our revenues since inception from collaborative research and development agreements. Revenues from research and development collaborations depend on research funding, the achievement of milestones, and royalties we earn from any future products developed from the collaborative research. If we are unable to successfully achieve milestones or our collaborators fail to develop successful products, we will not earn the revenues contemplated under such collaborative agreements. The amount of our net losses will depend, in part, on the rate of growth, if any, in our sales of COMETRIQ for progressive, metastatic MTC, license and contract revenues and on the level of our expenses. These losses have had and will continue to have an adverse effect on our stockholders' equity and working capital. Our research and development expenditures and general and administrative expenses have exceeded our revenues for each year other than 2011, and we expect to spend significant additional amounts to fund the continued development of cabozantinib. As a result, we expect to continue to incur substantial operating expenses, and, consequently, we will need to generate significant additional revenues to achieve future profitability. Because of the numerous risks and uncertainties associated with developing drugs, we are unable to predict the extent of any future losses or whether or when we will become profitable, if at all.

Our significant level of indebtedness could limit cash flow available for our operations and expose us to risks that could adversely affect our business, financial condition and results of operations.

We incurred significant additional indebtedness and substantial debt service requirements as a result of our offering of the 2019 Notes in August 2012. As of December 31, 2013, our total consolidated indebtedness through maturity was \$483.6 million (excluding trade payables). We may also incur additional indebtedness to meet future financing needs. If we incur additional indebtedness, it would increase our interest expense, leverage and operating and financial costs.

Our indebtedness could have significant negative consequences for our business, results of operations and financial condition, including:

making it more difficult for us to meet our payment and other obligations under the 2019 Notes, the Deerfield Notes, our loan and security agreement with Silicon Valley Bank or our other indebtedness;

resulting in an event of default if we fail to comply with the financial and other restrictive covenants contained in our debt agreements, which event of default could result in all of our debt becoming immediately due and payable;

increasing our vulnerability to adverse economic and industry conditions;

S-5

Table of Contents

subjecting us to the risk of increased sensitivity to interest rate increases on our indebtedness with variable interest rates, including borrowings under our loan and security agreement with Silicon Valley Bank;

limiting our ability to obtain additional financing;

requiring the dedication of a substantial portion of our cash flow from operations to service our indebtedness, thereby reducing the amount of our cash flow available for other purposes, including clinical trials, research and development, capital expenditures, working capital and other general corporate purposes;

limiting our flexibility in planning for, or reacting to, changes in our business;

preventing us from raising funds necessary to purchase the 2019 Notes in the event we are required to do so following a Fundamental Change as specified in the indenture governing the 2019 Notes, or to settle conversions of the 2019 Notes in cash;

dilution experienced by our existing stockholders as a result of the conversion of the 2019 Notes or the Deerfield Notes into shares of common stock; and

placing us at a possible competitive disadvantage with less leveraged competitors and competitors that may have better access to capital resources.

We cannot assure you that we will continue to maintain sufficient cash reserves or that our business will continue to generate cash flow from operations at levels sufficient to permit us to pay principal, premium, if any, and interest on our indebtedness, or that our cash needs will not increase. If we are unable to generate sufficient cash flow or otherwise obtain funds necessary to make required payments, or if we fail to comply with the various requirements of the 2019 Notes, the Deerfield Notes, our loan and security agreement with Silicon Valley Bank, or any indebtedness which we have incurred or may incur in the future, we would be in default, which would permit the holders or the Trustee of the 2019 Notes or other indebtedness to accelerate the maturity of such notes or other indebtedness and could cause defaults under the 2019 Notes, the Deerfield Notes, our loan and security agreement with Silicon Valley Bank or our other indebtedness. Any default under the 2019 Notes, the Deerfield Notes, our loan and security agreement with Silicon Valley Bank, or any indebtedness that we have incurred or may incur in the future could have a material adverse effect on our business, results of operations and financial condition.

If a Fundamental Change occurs, holders of the 2019 Notes may require us to purchase for cash all or any portion of their 2019 Notes at a purchase price equal to 100% of the principal amount of the Notes to be purchased plus accrued and unpaid interest, if any, to, but excluding, the Fundamental Change purchase date. We may not have sufficient funds to purchase the notes upon a Fundamental Change. In addition, the terms of any borrowing agreements which we may enter into from time to time may require early repayment of borrowings under circumstances similar to those constituting a Fundamental Change. Furthermore, any repurchase of 2019 Notes by us may be considered an event of default under such borrowing agreements.

We may not realize the expected benefits of our initiatives to control costs.

Managing costs is a key element of our business strategy. Consistent with this element of our strategy, and as a consequence of our decision to focus our proprietary resources and development efforts on the late-stage development and commercialization of cabozantinib, between March 2010 and May 2013 we implemented five restructurings, which resulted in an aggregate reduction in headcount of 429 employees. We have recorded aggregate restructuring charges of \$53.3 million from inception through December 31, 2013 in connection with the restructurings and anticipate that we will incur additional restructuring charges related to the exit of all or portions of certain of our buildings in South San Francisco, California. These charges will be recorded through the end of the building lease terms, the last of which ends in 2017.

S-6

Table of Contents

As part of these restructurings, we have entered into sublease agreements for certain of our facilities in South San Francisco. We are still assessing our ability to sublease portions of our facilities in light of the workforce reductions as well as the potential for sublease income. Estimates for sublease income would require significant assumptions regarding the time required to contract with subtenants, the amount of idle space we would be able to sublease and potential future sublease rates. If we are able to vacate portions of our facilities, we would need to continue to update our estimate of the lease exit costs in our financial statements until we were able to negotiate an exit to the lease or negotiate a sublease for the remaining term of the lease.

If we experience excessive unanticipated inefficiencies or incremental costs in connection with restructuring activities, such as unanticipated inefficiencies caused by reducing headcount, we may be unable to meaningfully realize cost savings and we may incur expenses in excess of what we anticipate. Either of these outcomes could prevent us from meeting our strategic objectives and could adversely impact our results of operations and financial condition.

We are exposed to risks related to foreign currency exchange rates.

Most of our foreign expenses incurred are associated with establishing and conducting clinical trials for cabozantinib. The amount of expenses incurred will be impacted by fluctuations in the currencies of those countries in which we conduct clinical trials. Our agreements with the foreign sites that conduct such clinical trials generally provide that payments for the services provided will be calculated in the currency of that country, and converted into U.S. dollars using various exchange rates based upon when services are rendered or the timing of invoices. When the U.S. dollar weakens against foreign currencies, the U.S. dollar value of the foreign-currency denominated expense increases, and when the U.S. dollar strengthens against these currencies, the U.S. dollar value of the foreign-currency denominated expense decreases. Consequently, changes in exchange rates may affect our financial position and results of operations.

Global credit and financial market conditions could negatively impact the value of our current portfolio of cash equivalents, short-term investments or long-term investments and our ability to meet our financing objectives.

Our cash and cash equivalents are maintained in highly liquid investments with remaining maturities of 90 days or less at the time of purchase. Our short-term and long-term investments consist primarily of readily marketable debt securities with remaining maturities of more than 90 days at the time of purchase. While as of the date of this prospectus supplement we are not aware of any downgrades, material losses, or other significant deterioration in the fair value of our cash equivalents, short-term investments or long-term investments since December 31, 2013, no assurance can be given that a deterioration in conditions of the global credit and financial markets would not negatively impact our current portfolio of cash equivalents or investments or our ability to meet our financing objectives.

We may not achieve expected benefits as a result of changes to our corporate structure.

During 2013, we engaged in intercompany transactions with a newly established wholly-owned foreign subsidiary pursuant to which such subsidiary acquired the existing and future intellectual property rights to exploit cabozantinib in jurisdictions outside of the United States, and we may establish additional wholly-owned foreign subsidiaries in the future. We established this structure in anticipation of an increase in the international nature of our business activities and to reduce our overall effective tax rate through changes in how we develop and use our intellectual property and the structure of our international procurement and sales, including by entering into transfer-pricing arrangements that establish transfer prices for our intercompany transactions. One of our objectives is to achieve a reduction in our overall effective tax rate in the future as a result. There can be no assurance that the taxing authorities of the jurisdictions in which we determine to operate or to which we will otherwise be deemed to have sufficient tax nexus

will not challenge the tax benefits that we expect to realize as a result of the new structure. In addition, future changes to U.S. or non-U.S. tax laws, including proposed legislation to reform U.S. taxation of international business activities, would negatively impact the anticipated tax benefits of the new structure. Any benefits to our tax rate will also depend on our ability to operate our business in a manner consistent with the new structure of our corporate organization and applicable taxing provisions, including by eliminating the amount of cash distributed to us by our subsidiaries. If the intended tax treatment is not accepted by the applicable taxing authorities, changes in tax law negatively impact the structure or we do not operate our business consistent with the new structure and applicable tax provisions, we may fail to achieve the financial efficiencies that we anticipate as a result of the changes to our corporate structure, and our future operating results and financial condition may be negatively impacted.

S-7

Table of Contents

Risks Related to COMETRIQ^(R) (cabozantinib)

We are dependent on the successful development and commercialization of COMETRIQ.

The success of our business is dependent upon the successful development and commercialization of COMETRIQ. As part of our strategy, we are dedicating substantially all of our proprietary resources to advance COMETRIQ as aggressively as possible. On November 29, 2012, the FDA approved COMETRIQ for the treatment of progressive, metastatic MTC in the United States and we commercially launched COMETRIQ in late January 2013. In December 2013, CHMP issued a positive opinion of the MAA, submitted to the EMA, for COMETRIQ for the proposed indication of progressive, unresectable, locally advanced, or metastatic MTC. The CHMP's positive opinion will be reviewed by the European Commission, which has the authority to approve medicines for the European Union. We view the approval of COMETRIQ by the FDA for the treatment of progressive, metastatic MTC as a transitional event towards our objective of developing COMETRIQ into a major oncology franchise. Our ability to realize this objective or the value of our investment is contingent on, among other things, successful clinical development, regulatory approval and market acceptance of COMETRIQ. If we encounter difficulties in the development of COMETRIQ in other indications beyond progressive, metastatic MTC due to any of the factors discussed in this Risk Factors section or otherwise, or we do not receive regulatory approval in such indications or are unable to successfully commercialize COMETRIQ in progressive, metastatic MTC or such other indications if approved, we will not have the resources necessary to continue our business in its current form.

The commercial success of COMETRIQ will depend upon the degree of market acceptance of COMETRIQ among physicians, patients, health care payors, and the medical community.

Our ability to commercialize COMETRIQ for the treatment of progressive, metastatic MTC and potentially other indications, if approved, will be highly dependent upon the extent to which COMETRIQ gains market acceptance among physicians, patients, health care payors such as Medicare and Medicaid, and the medical community. If COMETRIQ does not achieve an adequate level of acceptance, we may not generate significant future product revenues, and we may not become profitable. The degree of market acceptance of COMETRIQ will depend upon a number of factors, including:

the effectiveness, or perceived effectiveness, of COMETRIQ in comparison to competing products;

the existence of any significant side effects of COMETRIQ, as well as their severity in comparison to those of any competing products;

potential advantages or disadvantages in relation to alternative treatments;

the timing of market entry relative to competitive treatments;

indications for which COMETRIQ is approved;

the ability to offer COMETRIQ for sale at competitive prices;

S-8

Table of Contents

relative convenience and ease of administration;

the strength of sales, marketing and distribution support; and

sufficient third-party coverage or reimbursement.

If we are unable to establish and maintain adequate sales, marketing and distribution capabilities or enter into or maintain agreements with third parties to do so, we may be unable to successfully commercialize COMETRIQ.

We have established a small internal commercial organization that we believe is commensurate with the size of the market opportunity for progressive, metastatic MTC. We have also designed our commercial organization to maintain flexibility, and to enable us to quickly scale up if additional indications are approved in the future. We believe we have created an efficient commercial organization, taking advantage of outsourcing options where prudent to maximize the effectiveness of our commercial expenditures. However, we may not be able to correctly judge the size and experience of the sales and marketing force and the scale of distribution necessary to successfully market and sell COMETRIQ. Establishing and maintaining sales, marketing and distribution capabilities are expensive and time-consuming. Such expenses may be disproportional compared to the revenues we may be able to generate on sales of COMETRIQ and have an adverse impact on our results of operations. If we are unable to establish and maintain adequate sales, marketing and distribution capabilities, independently or with others, we may not be able to generate product revenues and our business may be adversely affected.

We currently rely on a single third party logistics provider to handle shipping and warehousing of our commercial supply of COMETRIQ and a single specialty pharmacy to dispense COMETRIQ to patients in fulfillment of prescriptions in the United States. We will also rely on a third party, Swedish Orphan Biovitrum, or Sobi, to distribute and commercialize COMETRIQ for the treatment of metastatic MTC primarily in the European Union and potentially other countries in the event that COMETRIQ is approved for commercial sale in those jurisdictions. Sobi is currently supporting access to cabozantinib under a Named Patient Use program in the European Union and other regions outside of the United States. Our current and anticipated future dependence upon these or other third parties may adversely affect our future profit margins and our ability to supply COMETRIQ to the marketplace on a timely and competitive basis. For example, if our third party logistics provider's warehouse suffers a fire or damage from another type of disaster, the commercial supply of COMETRIQ could be destroyed, resulting in a disruption in our commercialization efforts. These or other third parties may not be able to provide services in the time we require to meet our commercial timelines and objectives or to meet regulatory requirements. We may not be able to maintain or renew our arrangements with third parties, or enter into new arrangements, on acceptable terms, or at all. Third parties could terminate or decline to renew our arrangements based on their own business priorities, at a time that is costly or inconvenient for us. If we are unable to contract for logistics services or distribution of COMETRIQ on acceptable terms, our commercialization efforts may be delayed or otherwise adversely affected.

We are subject to certain healthcare laws, regulation and enforcement; our failure to comply with those laws could have a material adverse effect on our results of operations and financial condition.

We are subject to certain healthcare laws and regulations and enforcement by the federal government and the states in which we conduct our business. The laws that may affect our ability to operate include, without limitation:

the federal healthcare programs Anti-Kickback Law, which constrains our marketing practices, educational programs, pricing policies, and relationships with healthcare providers or other entities, by prohibiting, among other things, persons from knowingly and willfully soliciting, receiving, offering or paying remuneration, directly or indirectly, in exchange for or to induce either the referral of an individual for, or the purchase, order or recommendation of, any good or service for which payment may be made under federal healthcare programs such as the Medicare and Medicaid programs;

S-9

Table of Contents

federal civil and criminal false claims laws and civil monetary penalty laws, which prohibit, among other things, individuals or entities from knowingly presenting, or causing to be presented, claims for payment from Medicare, Medicaid, or other third-party payors that are false or fraudulent;

federal criminal laws that prohibit executing a scheme to defraud any healthcare benefit program or making false statements relating to healthcare matters;

state law equivalents of each of the above federal laws, such as anti-kickback and false claims laws which may apply to items or services reimbursed by any third-party payor, including commercial insurers, and state laws governing the privacy and security of health information in certain circumstances, many of which differ from each other in significant ways and may not have the same effect, thus complicating compliance efforts;

the Foreign Corrupt Practices Act, a U.S. law which regulates certain financial relationships with foreign government officials (which could include, for example, certain medical professionals);

federal and state consumer protection and unfair competition laws, which broadly regulate marketplace activities and activities that potentially harm consumers;

state and federal government price reporting laws that require us to calculate and report complex pricing metrics to government programs, where such reported prices may be used in the calculation of reimbursement and/or discounts on our marketed drugs (participation in these programs and compliance with the applicable requirements may subject us to potentially significant discounts on our products, increased infrastructure costs, and potentially limit our ability to offer certain marketplace discounts); and

state and federal marketing expenditure tracking and reporting laws, which generally require certain types of expenditures in the United States to be tracked and reported (compliance with such requirements may require investment in infrastructure to ensure that tracking is performed properly, and some of these laws result in the public disclosure of various types of payments and relationships, which could potentially have a negative effect on our business and/or increase enforcement scrutiny of our activities).

In addition, certain marketing practices, including off-label promotion, may also violate false claims laws. If our operations are found to be in violation of any of the laws described above or any other governmental regulations that apply to us, we, or our officers or employees, may be subject to penalties, including civil and criminal penalties, damages, fines, withdrawal of regulatory approval, the curtailment or restructuring of our operations, the exclusion from participation in federal and state healthcare programs and imprisonment, any of which could adversely affect our ability to sell COMETRIQ or operate our business and also adversely affect our financial results.

Numerous federal and state laws, including state security breach notification laws, state health information privacy laws and federal and state consumer protection laws, govern the collection, use and disclosure of personal information. Other countries also have, or are developing, laws governing the collection, use and transmission of

personal information. In addition, most healthcare providers who are expected to prescribe our products and from whom we obtain patient health information are subject to privacy and security requirements under the federal Health Insurance Portability and Accountability Act of 1996, or HIPAA. Although we are not directly subject to HIPAA, we could be subject to criminal penalties if we knowingly obtain individually identifiable health information from a HIPAA-covered entity in a manner that is not authorized or permitted by HIPAA. The legislative and regulatory landscape for privacy and data protection continues to evolve, and there has been an increasing amount of focus on privacy and data protection issues with the potential to affect our business, including recently enacted laws in a majority of states requiring security breach notification. These laws could create liability for us or increase our cost of doing business. International laws, such as the EU Data Privacy Directive (95/46/EC) and Swiss Federal Act on Data Protection, regulate the processing of personal data within Europe and between European countries and the United States. Failure to provide adequate privacy protections and maintain compliance with safe harbor mechanisms could jeopardize business transactions across borders and result in significant penalties.

S-10

Table of Contents

If we are unable to obtain adequate coverage and reimbursement from third-party payors for COMETRIQ, our revenues and prospects for profitability will suffer.

Our ability to successfully commercialize COMETRIQ will be highly dependent on the extent to which coverage and reimbursement for it is, and will be, available from third-party payors, including governmental payors, such as Medicare and Medicaid, and private health insurers. Many patients will not be capable of paying for COMETRIQ themselves and will rely on third-party payors to pay for, or subsidize, their medical needs. If third-party payors do not provide coverage or reimbursement for COMETRIQ, our revenues and prospects for profitability will suffer. In addition, even if third-party payors provide some coverage or reimbursement for COMETRIQ, the availability of such coverage or reimbursement for prescription drugs under private health insurance and managed care plans often varies based on the type of contract or plan purchased.

In addition, in some foreign countries, particularly the countries in the European Union, the pricing of prescription pharmaceuticals is subject to governmental control. In these countries, price negotiations with governmental authorities can take six to twelve months or longer after the receipt of regulatory marketing approval for a product. To obtain reimbursement and/or pricing approval in some countries, we may be required to conduct a clinical trial that compares the cost effectiveness of COMETRIQ to other available therapies. The conduct of such a clinical trial could be expensive and result in delays in the commercialization of COMETRIQ. Third-party payors are challenging the prices charged for medical products and services, and many third-party payors limit reimbursement for newly-approved health care products. In particular, third-party payors may limit the indications for which they will reimburse patients who use COMETRIQ. Cost-control initiatives could decrease the price we might establish for COMETRIQ, which would result in lower product revenues to us.

Current healthcare laws and regulations and future legislative or regulatory reforms to the healthcare system may affect our ability to sell COMETRIQ profitably.

The United States and some foreign jurisdictions are considering or have enacted a number of legislative and regulatory proposals to change the healthcare system in ways that could affect our ability to sell COMETRIQ profitably. Among policy makers and payors in the United States and elsewhere, there is significant interest in promoting changes in healthcare systems with the stated goals of containing healthcare costs, improving quality and/or expanding access. In the United States, the pharmaceutical industry has been a particular focus of these efforts and has been significantly affected by major legislative initiatives.

Table of Contents

For example, under the Patient Protection and Affordable Care Act, as amended by the Health Care and Education Affordability Reconciliation Act of 2010, collectively referred to as the PPACA, enacted in March 2010, substantial changes may be made to the way healthcare is financed by both governmental and private insurers, and those changes may significantly affect the pharmaceutical industry. Among other things, the PPACA creates a new system of health insurance exchanges, designed to make health policies available to individuals and certain groups through state- or federally-administered marketplaces, beginning in 2014. In connection with such exchanges, certain essential health benefits are intended to be made more consistent across plans, setting basically a baseline coverage level. While prescription drugs are broadly considered essential, there is some discretion to the plans as to what categories of prescription drug products will be covered (and the scope of coverage in each category). We cannot predict at this time whether COMETRIQ would be covered by the health plans offered in any or all of the exchanges. Failure to be covered by plans offered in the exchanges could have a material adverse impact on our business. We anticipate that the PPACA, as well as other healthcare reform measures that may be adopted in the future, may result in more rigorous coverage criteria and an additional downward pressure on the price that we receive for COMETRIQ and any subsequently approved product, and could seriously harm our business. Under the Budget Control Act of 2011, as amended, federal budget sequestration became effective in March 2013, automatically reducing payments under various government programs, including, for example, certain Medicare provider and supplier reimbursement payments. Sequestration may have a material adverse effect on our customers and accordingly, our financial operations. Any reduction in reimbursement from Medicare or other government programs may result in a similar reduction in payments from private payors. Insurers may also refuse to provide any coverage of uses of approved products for medical indications other than those for which the FDA has granted market approvals. As a result, significant uncertainty exists as to whether and how much third-party payors will reimburse for newly-approved drugs, which in turn will put pressure on the pricing of drugs.

We also cannot be certain that COMETRIQ will successfully be placed on the list of drugs covered by particular commercial or government health plan formularies, nor can we predict the negotiated price for COMETRIQ, which will be determined by market factors. Many states have also created preferred drug lists for their Medicaid programs, and include drugs on those lists only when the manufacturers agree to pay a supplemental rebate. If COMETRIQ is not included on these preferred drug lists, physicians may not be inclined to prescribe it to their Medicaid patients, thereby diminishing the potential market for COMETRIQ.

As a result of the overall trend towards cost-effectiveness criteria and managed healthcare in the United States, third-party payors are increasingly attempting to contain healthcare costs by limiting both coverage and the level of reimbursement of new drugs. They may use tiered reimbursement and may adversely affect demand for COMETRIQ by placing it in an expensive tier. They may also refuse to provide any coverage of uses of approved products for medical indications other than those for which the FDA has granted market approvals. As a result, significant uncertainty exists as to whether and how much third-party payors will reimburse for newly approved drugs, which in turn will put pressure on the pricing of drugs. Further, we do not have experience in ensuring approval by applicable third-party payors outside of the United States for coverage and reimbursement of COMETRIQ. We also anticipate pricing pressures in connection with the sale of COMETRIQ due to the increasing influence of health maintenance organizations and additional legislative proposals.

Table of Contents***Our competitors may develop products and technologies that make cabozantinib obsolete.***

The biotechnology industry is highly fragmented and is characterized by rapid technological change. In particular, the area of kinase-targeted therapies is a rapidly evolving and competitive field. We face, and will continue to face, intense competition from biotechnology and pharmaceutical companies, as well as academic research institutions, clinical reference laboratories and government agencies that are pursuing research activities similar to ours. Some of our competitors have entered into collaborations with leading companies within our target markets, including some of our existing collaborators. Some of our competitors are further along in the development of their products than we are. In addition, delays in the development of cabozantinib for the treatment of additional tumor types beyond progressive, metastatic MTC could allow our competitors to bring products to market before us, which would impair our ability to commercialize cabozantinib in such tumor types. Our future success will depend upon our ability to maintain a competitive position with respect to technological advances. The markets for which we intend to pursue regulatory approval of cabozantinib are highly competitive. Further, our competitors may be more effective at using their technologies to develop commercial products. Many of the organizations competing with us have greater capital resources, larger research and development staff and facilities, more experience in obtaining regulatory approvals and more extensive product manufacturing and commercial capabilities than we do. As a result, our competitors may be able to more easily develop technologies and products that would render our technologies and products, and those of our collaborators, obsolete and noncompetitive. There may also be drug candidates of which we are not aware at an earlier stage of development that may compete with cabozantinib. In addition, cabozantinib may compete with existing therapies that have long histories of use, such as chemotherapy and radiation treatments in cancer indications.

We believe that the principal competing anti-cancer therapy to COMETRIQ in progressive, metastatic MTC is AstraZeneca's RET, VEGFR and EGFR inhibitor vandetanib, which has been approved by the FDA and the EMA for the treatment of symptomatic or progressive MTC in patients with unresectable, locally advanced, or metastatic disease. In addition, we believe that COMETRIQ also faces competition as a treatment for progressive, metastatic MTC from off-label use of Bayer's and Onyx Pharmaceuticals (a wholly-owned subsidiary of Amgen) multikinase inhibitor sorafenib, Pfizer's multikinase inhibitor sunitinib, and Ariad Pharmaceutical's multikinase inhibitor ponatinib.

We believe that if cabozantinib is approved for the treatment of the indications for which we currently have ongoing phase 3 pivotal trials, its potential principal competition in such indications may include the following:

CRPC (castration-resistant prostate cancer): Bayer's and Algeta's alpha-pharmaceutical alpharadin (radium 223); Janssen Biotech's CYP17 inhibitor abiraterone; Medivation's androgen receptor inhibitor enzalutamide; and chemotherapeutic agents, including Sanofi's cabazitaxel and generic docetaxel;

RCC (renal cell cancer): Pfizer's axitinib, sunitinib and temsirolimus; Novartis' everolimus; Bayer's and Onyx Pharmaceuticals' sorafenib; GlaxoSmithKline's pazopanib; and Genentech's bevacizumab; and

HCC (hepatocellular): Bayer's and Onyx Pharmaceuticals' sorafenib; Bayer's regorafenib; ImClone System's ramucirumab; and ArQule's tivantinib.

Examples of potential competition for cabozantinib in other cancer indications include: other VEGF pathway inhibitors, including Genentech's bevacizumab; other RET inhibitors including Eisai's lenvatinib; and other MET inhibitors, including Amgen's AMG 208, Pfizer's crizotinib, ArQule's tivantinib, GlaxoSmithKline's foretinib (XL880), and Genentech's onartuzumab.

S-13

Table of Contents

We lack the manufacturing capabilities and experience necessary to enable us to produce COMETRIQ for clinical development or for commercial sale and rely on third parties to do so, which subjects us to various risks.

We do not have the manufacturing capabilities or experience necessary to enable us to produce materials for our clinical trials or for commercial sale of COMETRIQ and rely on third party contractors to do so. These third parties must comply with applicable regulatory requirements, including the FDA's current Good Manufacturing Practices, or GMP. Our current and anticipated future dependence upon these third parties may adversely affect our future profit margins and our ability to develop and commercialize COMETRIQ on a timely and competitive basis. These third parties may not be able to produce material on a timely basis or manufacture material at the quality or in the quantity required to meet our development and commercial timelines and applicable regulatory requirements. We may not be able to maintain or renew our existing third party manufacturing and supply arrangements, or enter into new arrangements, on acceptable terms, or at all. Our third party manufacturers and suppliers could terminate or decline to renew our manufacturing and supply arrangements based on their own business priorities, at a time that is costly or inconvenient for us. If we are unable to contract for the production of materials in sufficient quantity and of sufficient quality on acceptable terms, our clinical trials and commercialization efforts may be delayed or otherwise adversely affected.

Our third-party manufacturers may not be able to comply with the GMP regulations, other applicable FDA regulatory requirements or similar regulations applicable outside of the United States. Additionally, if we are required to enter into new manufacturing or supply arrangements, we may not be able to obtain approval from the FDA of any alternate manufacturer or supplier in a timely manner, or at all, which could delay or prevent the clinical development and commercialization of COMETRIQ. Failure of our third party manufacturers or suppliers or us to obtain approval from the FDA or to comply with applicable regulations could result in sanctions being imposed on us, including fines, civil penalties, delays in or failure to grant marketing approval of COMETRIQ, injunctions, delays, suspension or withdrawal of approvals, license revocation, seizures or recalls of products and compounds, operating restrictions and criminal prosecutions, any of which could have a significant adverse effect on our business. In addition, COMETRIQ requires precise, high-quality manufacturing. The failure to achieve and maintain these high manufacturing standards, including the incidence of manufacturing errors, could result in patient injury or death, product recalls or withdrawals, delays or failures in product testing or delivery, cost overruns or other problems that could have also a significant adverse effect on our business.

Clinical testing of cabozantinib is a lengthy, costly, complex and uncertain process and may fail to demonstrate safety and efficacy.

Cabozantinib is being evaluated in a comprehensive development program for the treatment of CRPC, RCC, HCC and a variety of other indications beyond progressive, metastatic MTC. Clinical trials are inherently risky and may reveal that cabozantinib is ineffective or has unacceptable toxicity or other side effects that may significantly decrease the likelihood of regulatory approval in such indications.

The results of preliminary studies do not necessarily predict clinical or commercial success, and later-stage clinical trials may fail to confirm the results observed in earlier-stage trials or preliminary studies. Although we have established timelines for manufacturing and clinical development of cabozantinib based on existing knowledge of our compounds in development and industry metrics, we may not be able to meet those timelines.

We may experience numerous unforeseen events during, or as a result of, clinical testing that could delay or prevent commercialization of cabozantinib for the treatment of CRPC, RCC, HCC and other indications, including:

cabozantinib may not prove to be efficacious or may cause, or potentially cause, harmful side effects;

S-14

Table of Contents

negative or inconclusive clinical trial results may require us to conduct further testing or to abandon projects that we had expected to be promising;

our competitors may discover or commercialize other compounds or therapies that show significantly improved safety or efficacy compared to cabozantinib;

patient registration or enrollment in our clinical testing may be lower than we anticipate, resulting in the delay or cancellation of clinical testing; and

regulators or institutional review boards may withhold authorization of cabozantinib, or delay, suspend or terminate clinical research for various reasons, including noncompliance with regulatory requirements or their determination that participating patients are being exposed to unacceptable health risks.

If we were to have significant delays in or termination of our clinical testing of cabozantinib as a result of any of the events described above or otherwise, our expenses could increase and our ability to generate revenues could be impaired, either of which could adversely impact our financial results.

We have limited experience in conducting clinical trials and may not be able to rapidly or effectively continue the further development of cabozantinib or meet current or future requirements of the FDA or regulatory authorities in other jurisdictions, including those identified based on our discussions with the FDA or such other regulatory authorities. Our planned clinical trials may not begin on time, or at all, may not be completed on schedule, or at all, may not be sufficient for registration of cabozantinib or may not result in an approvable product.

Completion of clinical trials may take several years or more, but the length of time generally varies substantially according to the type, complexity, novelty and intended use of cabozantinib. The duration and the cost of clinical trials may vary significantly over the life of a project as a result of factors relating to the clinical trial, including, among others:

the number of patients who ultimately participate in the clinical trial;

the duration of patient follow-up that is appropriate in view of the results or required by regulatory authorities;

the number of clinical sites included in the trials; and

the length of time required to enroll suitable patient subjects.

Any delay could limit our ability to generate revenues, cause us to incur additional expense and cause the market price of our common stock to decline significantly. Our partners under our collaboration agreements may experience similar risks with respect to the compounds we have out-licensed to them. If any of the events described above were to occur with such programs or compounds, the likelihood of receipt of milestones and royalties under such collaboration

agreements could decrease.

If third parties upon which we rely do not perform as contractually required or expected, we may not be able to obtain regulatory approval for or commercialize cabozantinib for the treatment of additional indications beyond progressive, metastatic MTC.

We do not have the ability to independently conduct clinical trials for cabozantinib, including our postmarketing commitments for COMETRIQ for the treatment of progressive, metastatic MTC, and we rely on third parties we do not control such as the federal government (including NCI-CTEP, with whom we have our CRADA), third-party contract research organizations, or CROs, medical institutions, clinical investigators and contract laboratories to conduct our clinical trials. If these third parties do not successfully carry out their contractual duties or regulatory obligations or meet expected deadlines, if the third parties need to be replaced or if the quality or accuracy of the data they obtain is compromised due to the failure to adhere to our clinical protocols or regulatory requirements or for other reasons, our preclinical development activities or clinical trials may be extended, delayed, suspended or terminated, and we may not be able to obtain regulatory approval for or commercialize cabozantinib for additional indications beyond progressive, metastatic MTC.

S-15

Table of Contents

Cabozantinib is subject to a lengthy and uncertain regulatory process that may not result in the necessary regulatory approvals, which could adversely affect our ability to commercialize cabozantinib.

Cabozantinib, as well as the activities associated with its research, development and commercialization, are subject to extensive regulation by the FDA and other regulatory agencies in the United States and by comparable authorities in other countries. Failure to obtain regulatory approval for cabozantinib would prevent us from promoting its use. We have only limited experience in preparing and filing the applications necessary to gain regulatory approvals. The process of obtaining regulatory approvals in the United States and other foreign jurisdictions is expensive, and often takes many years, if approval is obtained at all, and can vary substantially based upon the type, complexity and novelty of the product candidates involved. For example, before a New Drug Application, or NDA, or NDA supplement can be submitted to the FDA, or MAA to the EMA or any application or submission to regulatory authorities in other jurisdictions, the product candidate must undergo extensive clinical trials, which can take many years and require substantial expenditures.

In December 2011, we initiated COMET-2, our first phase 3 pivotal trial of cabozantinib in patients with metastatic CRPC, with pain response as the primary efficacy endpoint for the trial. We were not able to reach a timely agreement with the FDA for a Special Protocol Assessment, or SPA, on the proposed design and analysis of the COMET-2 trial. We originally submitted the proposed protocol for this trial using primary endpoints of pain reduction and bone scan response to the FDA in June 2011 with a request for a SPA. The FDA's final response prior to our discontinuation of the SPA process, which we received in October 2011, raised the following concerns regarding the COMET-2 trial design in the context of its consideration of a SPA for the trial, among other comments:

a concern about the ability to maintain blinding of the trial due to differences in toxicity profiles between cabozantinib and mitoxantrone;

a view that the assumed magnitude of pain improvement is modest and could represent a placebo effect or be attained with less toxicity by opioid therapy;

a view that symptomatic improvement should be supported by evidence of anti-tumor activity, an acceptable safety profile and lack of survival decrement. The FDA also expressed the view that if the effect that we believe cabozantinib will have on pain is mediated by anti-tumor activity, that anti-tumor activity should translate into an improvement in overall survival; and

a recommendation that if we use pain response as a primary efficacy endpoint, that we conduct two adequate and well-controlled trials to demonstrate effectiveness as, according to the FDA, a conclusion based on two persuasive studies will always be more secure. The FDA advised that for a single randomized trial to support an NDA, the trial must be well designed, well conducted, internally consistent and provide statistically persuasive efficacy findings so that a second trial would be ethically or practically impossible to perform.

In the context of its consideration of a SPA for the COMET-2 trial, the FDA also recommended that overall survival be the primary efficacy endpoint. The final FDA response prior to our discontinuation of the SPA process stated that we could choose to conduct the trial in the absence of a SPA agreement. We elected to proceed with initiation of the COMET-2 trial and the COMET-1 trial, and to discontinue further attempts to secure a SPA agreement with respect to

the COMET-2 trial. We initiated the COMET-2 trial with a pain palliation endpoint in December 2011 and the COMET-1 trial with an overall survival endpoint in May 2012.

S-16

Table of Contents

Any clinical trial may fail to produce results satisfactory to the FDA or regulatory authorities in other jurisdictions. For example, the FDA could determine that the design of a clinical trial is inadequate to produce reliable results. The regulatory process also requires preclinical testing, and data obtained from preclinical and clinical activities are susceptible to varying interpretations. The FDA has substantial discretion in the approval process and may refuse to approve any NDA (regardless of prior receipt of a SPA) or decide that our data is insufficient for approval and require additional preclinical, clinical or other studies. For example, varying interpretations of the data obtained from preclinical and clinical testing could delay, limit or prevent regulatory approval of cabozantinib.

In addition, delays or rejections may be encountered based upon changes in regulatory policy for product approval during the period of product development and regulatory agency review. Changes in regulatory approval policy, regulations or statutes or the process for regulatory review during the development or approval periods of cabozantinib may cause delays in the approval or rejection of an application.

Even if the FDA or a comparable authority in another jurisdiction approves cabozantinib, the approval may impose significant restrictions on the indicated uses, conditions for use, labeling, distribution, advertising, promotion, marketing and/or production of cabozantinib and may impose ongoing requirements for post-approval studies, including additional research and development and clinical trials. For example, in connection with the FDA's approval of COMETRIQ for the treatment of progressive, metastatic MTC, we are subject to the various postmarketing requirements, including a requirement to conduct a phase 2 clinical trial comparing a lower dose of COMETRIQ to the approved dose of 140 mg daily COMETRIQ in progressive, metastatic MTC and to conduct other clinical pharmacology and preclinical studies. These agencies also may impose various civil or criminal sanctions for failure to comply with regulatory requirements, including withdrawal of product approval.

Risks Related to Our Relationships with Third Parties

We are dependent upon our collaborations with major companies, which subjects us to a number of risks.

We have established collaborations with leading pharmaceutical and biotechnology companies, including Genentech, GlaxoSmithKline, Bristol-Myers Squibb, Sanofi, Merck (known as MSD outside of the United States and Canada) and Daiichi Sankyo, for the development and ultimate commercialization of certain compounds generated from our research and development efforts. We may pursue collaborations for selected unpartnered preclinical and clinical programs and compounds. Our dependence on our relationships with existing collaborators for the development and commercialization of compounds under the collaborations subjects us to, and our dependence on future collaborators for development and commercialization of additional compounds will subject us to, a number of risks, including:

we may not be able to control the amount of U.S. marketing and commercialization costs for cobimetinib we are obligated to share under our collaboration with Genentech;

we are not able to control the amount and timing of resources that our collaborators or potential future collaborators will devote to the development or commercialization of drug candidates or to their marketing and distribution;

collaborators may delay clinical trials, provide insufficient funding for a clinical trial program, stop a clinical trial or abandon a drug candidate, repeat or conduct new clinical trials or require a new

formulation of a drug candidate for clinical testing;

disputes may arise between us and our collaborators that result in the delay or termination of the research, development or commercialization of our drug candidates or that result in costly litigation or arbitration that diverts management's attention and resources;

S-17

Table of Contents

collaborators may experience financial difficulties;

collaborators may not be successful in their efforts to obtain regulatory approvals in a timely manner, or at all;

collaborators may not properly maintain or defend our intellectual property rights or may use our proprietary information in such a way as to invite litigation that could jeopardize or invalidate our proprietary information or expose us to potential litigation;

business combinations or significant changes in a collaborator's business strategy may adversely affect a collaborator's willingness or ability to complete its obligations under any arrangement;

a collaborator could independently move forward with a competing drug candidate developed either independently or in collaboration with others, including our competitors;

we may be precluded from entering into additional collaboration arrangements with other parties in an area or field of exclusivity;

future collaborators may require us to relinquish some important rights, such as marketing and distribution rights; and

collaborations may be terminated or allowed to expire, which would delay, and may increase the cost of development of, our drug candidates.

If any of these risks materialize, our product development efforts could be delayed and otherwise adversely affected, which could adversely impact our business, operating results and financial condition.

We may not receive revenue from our collaborations.

Historically, we have derived substantially all of our revenues since inception from collaborative research and development agreements. Revenues from research and development collaborations depend on the achievement of milestones, and royalties we earn from any future products developed by our collaborators. If our collaborators fail to develop successful products, or if any of these agreements is terminated early, whether unilaterally or by mutual agreement, we will not earn the revenues contemplated under such collaborative agreements.

Most of our collaboration agreements contain early termination provisions. In addition, from time to time we review and assess certain aspects of our collaborations, partnerships and agreements and may amend or terminate, either by mutual agreement or pursuant to any applicable early termination provisions, such collaborations, partnerships or agreements if we deem them to be no longer in our economic or strategic interests.

We may be unable to establish collaborations for selected preclinical and clinical compounds.

We may pursue new collaborations with leading pharmaceutical and biotechnology companies for the development and ultimate commercialization of selected preclinical and clinical programs and compounds, particularly those drug candidates for which we believe that the capabilities and resources of a partner can accelerate development and help to fully realize their therapeutic and commercial potential. We may not be able to negotiate additional collaborations on acceptable terms, or at all. We are unable to predict when, if ever, we will enter into any additional collaborations because of the numerous risks and uncertainties associated with establishing additional collaborations. If we are unable to negotiate additional collaborations, we may not be able to realize value from a particular drug candidate.

S-18

Table of Contents**Risks Related to Our Intellectual Property**

If we are unable to adequately protect our intellectual property, third parties may be able to use our technology, which could adversely affect our ability to compete in the market.

Our success will depend in part upon our ability to obtain patents and maintain adequate protection of the intellectual property related to our technologies and products. The patent positions of biotechnology companies, including our patent position, are generally uncertain and involve complex legal and factual questions. We will be able to protect our intellectual property rights from unauthorized use by third parties only to the extent that our technologies are covered by valid and enforceable patents or are effectively maintained as trade secrets. We will continue to apply for patents covering our technologies and products as, where and when we deem appropriate. However, these applications may be challenged or may fail to result in issued patents. In addition, because patent applications can take many years to issue, there may be pending applications, unknown to us, which may later result in issued patents that cover the production, manufacture, commercialization or use of our product candidates. Our existing patents and any future patents we obtain may not be sufficiently broad to prevent others from practicing our technologies or from developing competing products. Furthermore, others may independently develop similar or alternative technologies or design around our patents. In addition, our patents may be challenged or invalidated or may fail to provide us with any competitive advantages, if, for example, others were the first to invent or to file patent applications for closely related inventions.

The laws of some foreign countries do not protect intellectual property rights to the same extent as the laws of the United States, and many companies have encountered significant problems in protecting and defending such rights in foreign jurisdictions. Many countries, including certain countries in Europe, have compulsory licensing laws under which a patent owner may be compelled to grant licenses to third parties (for example, the patent owner has failed to work the invention in that country or the third party has patented improvements). In addition, many countries limit the enforceability of patents against government agencies or government contractors. In these countries, the patent owner may have limited remedies, which could materially diminish the value of the patent. Compulsory licensing of life-saving drugs is also becoming increasingly popular in developing countries either through direct legislation or international initiatives. Such compulsory licenses could be extended to include our products or product candidates, which could limit our potential revenue opportunities. Moreover, the legal systems of certain countries, particularly certain developing countries, do not favor the aggressive enforcement of patent and other intellectual property protection, which makes it difficult to stop infringement. We rely on trade secret protection for some of our confidential and proprietary information. We have taken security measures to protect our proprietary information and trade secrets, but these measures may not provide adequate protection. While we seek to protect our proprietary information by entering into confidentiality agreements with employees, collaborators and consultants, we cannot assure you that our proprietary information will not be disclosed, or that we can meaningfully protect our trade secrets. In addition, our competitors may independently develop substantially equivalent proprietary information or may otherwise gain access to our trade secrets.

Litigation or third-party claims of intellectual property infringement could require us to spend substantial time and money and adversely affect our ability to develop and commercialize products.

Our commercial success depends in part upon our ability to avoid infringing patents and proprietary rights of third parties and not to breach any licenses that we have entered into with regard to our technologies and the technologies of third parties. Other parties have filed, and in the future are likely to file, patent applications covering genes and gene fragments, techniques and methodologies relating to model systems and products and technologies that we have developed or intend to develop. If patents covering technologies required by our operations are issued to others, we may have to obtain licenses from third parties, which may not be available on commercially reasonable terms, or at

all, and may require us to pay substantial royalties, grant a cross-license to some of our patents to another patent holder or redesign the formulation of a product candidate so that we do not infringe third-party patents, which may be impossible to obtain or could require substantial time and expense.

S-19

Table of Contents

Third parties may accuse us of employing their proprietary technology without authorization. In addition, third parties may obtain patents that relate to our technologies and claim that use of such technologies infringes on their patents. Regardless of their merit, such claims could require us to incur substantial costs, including the diversion of management and technical personnel, in defending ourselves against any such claims or enforcing our patents. In the event that a successful claim of infringement is brought against us, we may be required to pay damages and obtain one or more licenses from third parties. We may not be able to obtain these licenses at a reasonable cost, or at all. Defense of any lawsuit or failure to obtain any of these licenses could adversely affect our ability to develop and commercialize products.

We may be subject to damages resulting from claims that we, our employees or independent contractors have wrongfully used or disclosed alleged trade secrets of their former employers.

Many of our employees and independent contractors were previously employed at universities or other biotechnology or pharmaceutical companies, including our competitors or potential competitors. We may be subject to claims that these employees, independent contractors or we have inadvertently or otherwise used or disclosed trade secrets or other proprietary information of their former employers, or used or sought to use patent inventions belonging to their former employers. Litigation may be necessary to defend against these claims. Even if we are successful in defending against these claims, litigation could result in substantial costs and divert management's attention. If we fail in defending such claims, in addition to paying money claims, we may lose valuable intellectual property rights or personnel. A loss of key research personnel and/or their work product could hamper or prevent our ability to commercialize certain product candidates, which could severely harm our business.

Risks Related to Employees and Location

The loss of key personnel or the inability to retain and, where necessary, attract additional personnel could impair our ability to expand our operations.

We are highly dependent upon the principal members of our management and scientific staff, the loss of whose services might adversely impact the achievement of our objectives and the continuation of existing collaborations. Also, we may not have sufficient personnel to execute our business plan. Retaining and, where necessary, recruiting qualified clinical and scientific personnel will be critical to support activities related to advancing our clinical and preclinical development programs, and supporting our collaborative arrangements and our internal proprietary research and development efforts. The restructurings we have engaged in could have an adverse impact on our ability to retain and recruit qualified personnel. Competition is intense for experienced clinical personnel, and we may be unable to retain or recruit clinical personnel with the expertise or experience necessary to allow us to pursue collaborations, develop our products and core technologies or expand our operations to the extent otherwise possible. Further, all of our employees are employed at will and, therefore, may leave our employment at any time.

Our collaborations with outside scientists may be subject to restriction and change.

We work with scientific and clinical advisors and collaborators at academic and other institutions that assist us in our research and development efforts. These advisors and collaborators are not our employees and may have other commitments that limit their availability to us. Although these advisors and collaborators generally agree not to do competing work, if a conflict of interest between their work for us and their work for another entity arises, we may lose their services. In such a circumstance, we may lose work performed by them, and our development efforts with respect to the matters on which they were working may be significantly delayed or otherwise adversely affected. In addition, although our advisors and collaborators sign agreements not to disclose our confidential information, it is possible that valuable proprietary knowledge may become publicly known through them.

S-20

Table of Contents

Our headquarters are located near known earthquake fault zones, and the occurrence of an earthquake or other disaster could damage our facilities and equipment, which could harm our operations.

Our headquarters are located in South San Francisco, California, and therefore our facilities are vulnerable to damage from earthquakes. We do not carry earthquake insurance. We are also vulnerable to damage from other types of disasters, including fire, floods, power loss, communications failures, terrorism and similar events since any insurance we may maintain may not be adequate to cover our losses. If any disaster were to occur, our ability to operate our business at our facilities could be seriously, or potentially completely, impaired. In addition, the unique nature of our research activities could cause significant delays in our programs and make it difficult for us to recover from a disaster. Accordingly, an earthquake or other disaster could materially and adversely harm our ability to conduct business.

Security breaches may disrupt our operations, subject us to liability and harm our operating results.

Our network security and data recovery measures may not be adequate to protect against computer viruses, break-ins, and similar disruptions from unauthorized tampering with our computer systems. The misappropriation, theft, sabotage or any other type of security breach with respect to any of our proprietary and confidential information that is electronically stored, including research or clinical data, could subject us to liability and have a material adverse impact on our business, operating results and financial condition. Additionally, any break-in or trespass at our facilities that results in the misappropriation, theft, sabotage or any other type of security breach with respect to our proprietary and confidential information, including research or clinical data, or that results in damage to our research and development equipment and assets, could subject us to liability and have a material adverse impact on our business, operating results and financial condition.

Risks Related to Environmental and Product Liability

We use hazardous chemicals and radioactive and biological materials in our business. Any claims relating to improper handling, storage or disposal of these materials could be time consuming and costly.

Our research and development processes involve the controlled use of hazardous materials, including chemicals and radioactive and biological materials. Our operations produce hazardous waste products. We cannot eliminate the risk of accidental contamination or discharge and any resultant injury from these materials. Federal, state and local laws and regulations govern the use, manufacture, storage, handling and disposal of hazardous materials. We may face liability for any injury or contamination that results from our use or the use by third parties of these materials, and such liability may exceed our insurance coverage and our total assets. Compliance with environmental laws and regulations may be expensive, and current or future environmental regulations may impair our research, development and production efforts.

In addition, our collaborators may use hazardous materials in connection with our collaborative efforts. In the event of a lawsuit or investigation, we could be held responsible for any injury caused to persons or property by exposure to, or release of, these hazardous materials used by these parties. Further, we may be required to indemnify our collaborators against all damages and other liabilities arising out of our development activities or products produced in connection with these collaborations.

Table of Contents

We face potential product liability exposure far in excess of our limited insurance coverage.

We may be held liable if any product we or our collaborators develop causes injury or is found otherwise unsuitable during product testing, manufacturing, marketing or sale. Regardless of merit or eventual outcome, product liability claims could result in decreased demand for our product candidates, injury to our reputation, withdrawal of patients from our clinical trials, substantial monetary awards to third parties and the inability to commercialize any products that we may develop. These claims might be made directly by consumers, health care providers, pharmaceutical companies or others selling or testing our products. We have obtained limited product liability insurance coverage for our clinical trials and commercial activities for cabozantinib in the amount of \$15.0 million per occurrence and \$15.0 million in the aggregate. However, our insurance may not reimburse us or may not be sufficient to reimburse us for expenses or losses we may suffer. Moreover, if insurance coverage becomes more expensive, we may not be able to maintain insurance coverage at a reasonable cost or in sufficient amounts to protect us against losses due to liability. On occasion, juries have awarded large judgments in class action lawsuits for claims based on drugs that had unanticipated side effects. In addition, the pharmaceutical and biotechnology industries, in general, have been subject to significant medical malpractice litigation. A successful product liability claim or series of claims brought against us could harm our reputation and business and would decrease our cash reserves.

Risks Related to Our Common Stock and the 2019 Notes

We expect that our quarterly results of operations will fluctuate, and this fluctuation could cause our stock price to decline, causing investor losses.

Our quarterly operating results have fluctuated in the past and are likely to fluctuate in the future. A number of factors, many of which we cannot control, could subject our operating results to volatility, including:

the progress and scope of our development and commercialization activities;

the commercial success of COMETRIQ and the revenues we generate;

recognition of upfront licensing or other fees or revenues;

payments of non-refundable upfront or licensing fees, or payment for cost-sharing expenses, to third parties;

acceptance of our technologies and platforms;

the success rate of our efforts leading to milestone payments and royalties;

the introduction of new technologies or products by our competitors;

the timing and willingness of collaborators to further develop or, if approved, commercialize our product candidates out-licensed to them;

our ability to enter into new collaborative relationships;

the termination or non-renewal of existing collaborations;

the timing and amount of expenses incurred for clinical development and manufacturing of cabozantinib;

adjustments to expenses accrued in prior periods based on management's estimates after the actual level of activity relating to such expenses becomes more certain;

the impairment of acquired goodwill and other assets;

the impact of our restructuring activities; and

general and industry-specific economic conditions that may affect our collaborators' research and development expenditures.

A large portion of our expenses, including expenses for facilities, equipment and personnel, are relatively fixed in the short term. If we fail to achieve anticipated levels of revenues, whether due to the expiration or termination of existing contracts, our failure to obtain new contracts, our inability to meet milestones or for other reasons, we may not be able to correspondingly reduce our operating expenses, which could significantly harm our operating results for a particular fiscal period.

Table of Contents

Due to the possibility of fluctuations in our revenues and expenses, we believe that quarter-to-quarter comparisons of our operating results are not a good indication of our future performance. As a result, in some future quarters, our operating results may not meet the expectations of securities analysts and investors, which could result in a decline in the price of our common stock.

Our stock price may be extremely volatile.

The trading price of our common stock has been highly volatile, and we believe the trading price of our common stock will remain highly volatile and may fluctuate substantially due to factors such as the following, many of which we cannot control:

adverse results or delays in our or our collaborators' clinical trials;

announcement of FDA approval or non-approval, or delays in the FDA review process, of cabozantinib or our collaborators' product candidates or those of our competitors or actions taken by regulatory agencies with respect to our, our collaborators' or our competitors' clinical trials;

the commercial success of COMETRIQ and the revenues we generate;

the timing of achievement of our clinical, regulatory, partnering and other milestones, such as the commencement of clinical development, the completion of a clinical trial, the filing for regulatory approval or the establishment of collaborative arrangements for one or more of our out-licensed programs and compounds;

actions taken by regulatory agencies with respect to cabozantinib or our clinical trials for cabozantinib;

the announcement of new products by our competitors;

quarterly variations in our or our competitors' results of operations;

developments in our relationships with our collaborators, including the termination or modification of our agreements;

conflicts or litigation with our collaborators;

litigation, including intellectual property infringement and product liability lawsuits, involving us;

failure to achieve operating results projected by securities analysts;

changes in earnings estimates or recommendations by securities analysts;

financing transactions;

developments in the biotechnology or pharmaceutical industry;

sales of large blocks of our common stock or sales of our common stock by our executive officers, directors and significant stockholders;

departures of key personnel or board members;

developments concerning current or future collaborations;

FDA or international regulatory actions;

third-party reimbursement policies;

disposition of any of our subsidiaries, technologies or compounds; and

general market, economic and political conditions and other factors, including factors unrelated to our operating performance or the operating performance of our competitors.

Table of Contents

These factors, as well as general economic, political and market conditions, may materially adversely affect the market price of our common stock. Excessive volatility may continue for an extended period of time following the date of this prospectus supplement.

In the past, following periods of volatility in the market price of a company's securities, securities class action litigation has often been instituted. A securities class action suit against us could result in substantial costs and divert management's attention and resources, which could have a material and adverse effect on our business.

Future sales of our common stock or conversion of our convertible notes, or the perception that such sales or conversions may occur, may depress our stock price.

A substantial number of shares of our common stock is reserved for issuance upon conversion of the 2019 Notes, upon the exercise of stock options, upon vesting of restricted stock unit awards, upon sales under our employee stock purchase program, upon exercise of certain warrants issued to Deerfield and upon conversion of the Deerfield Notes. The issuance and sale of substantial amounts of our common stock, including upon conversion of the 2019 Notes or the Deerfield Notes, or the perception that such issuances and sales may occur, could adversely affect the market price of our common stock and impair our ability to raise capital through the sale of additional equity or equity-related securities in the future at a time and price that we deem appropriate. Trading of the 2019 Notes is likely to influence and be influenced by the market for our common stock. For example, the price of our common stock could be affected by possible sales of common stock by investors who view the 2019 Notes as a more attractive means of equity participation in our company and by hedging or arbitrage trading activity that we expect to occur involving our common stock.

The accounting method for convertible debt securities that may be settled in cash, such as the 2019 Notes, could have a material effect on our reported financial results.

Under Accounting Standards Codification, or ASC, Subtopic 470-20, issuers of certain convertible debt instruments that have a net settlement feature and may be settled in cash upon conversion, including partial cash settlement, are required to separately account for the liability (debt) and equity (conversion option) components of the instrument. As a result of the application of ASC 470-20, we recognized \$143.2 million as the initial debt discount with a corresponding increase to paid-in capital, the equity component, for the 2019 Notes. We will be required to record the amortization of this debt discount over the terms of the 2019 Notes, which may adversely affect our reported or future financial results and the market price of our common stock. In addition, if the 2019 Notes become convertible, we could be required under applicable accounting rules to reclassify all or a portion of the outstanding principal of the 2019 Notes as a current rather than long-term liability, which would result in a material reduction of our net working capital. Finally, we use the if-converted method to compute earnings per share, which could be more dilutive than using the treasury stock method.

Certain provisions applicable to the 2019 Notes and the Deerfield Notes could delay or prevent an otherwise beneficial takeover or takeover attempt

Certain provisions applicable to the 2019 Notes and the indenture pursuant to which the 2019 Notes were issued, and the Deerfield Notes and the note purchase agreement governing the Deerfield Notes, could make it more difficult or more expensive for a third party to acquire us. For example, if an acquisition event constitutes a Fundamental Change under the indenture for the 2019 Notes or a Major Transaction under the note purchase agreement governing the Deerfield Notes, holders of the 2019 Notes or the Deerfield Notes, applicable, will have the right to require us to purchase their notes in cash. In addition, if an acquisition event constitutes a Make-Whole Fundamental Change under the indenture for the 2019 Notes, we may be required to increase the conversion rate for holders who convert their

2019 Notes in connection with such Make-Whole Fundamental Change. In any of these cases, and in other cases, our obligations under the 2019 Notes and the indenture pursuant to which such notes were issued and the Deerfield Notes and the note purchase agreement governing the Deerfield Notes, as well as provisions of our organizational documents and other agreements, could increase the cost of acquiring us or otherwise discourage a third party from acquiring us or removing incumbent management.

S-24

Table of Contents

Anti-takeover provisions in our charter documents and under Delaware law could make an acquisition of us, which may be beneficial to our stockholders, more difficult and may prevent or deter attempts by our stockholders to replace or remove our current management, which could cause the market price of our common stock to decline.

Provisions in our corporate charter and bylaws may discourage, delay or prevent an acquisition of our company, a change in control, or attempts by our stockholders to replace or remove members of our current Board of Directors. Because our Board of Directors is responsible for appointing the members of our management team, these provisions could in turn affect any attempt by our stockholders to replace current members of our management team. These provisions include:

a classified Board of Directors;

a prohibition on actions by our stockholders by written consent;

the inability of our stockholders to call special meetings of stockholders;

the ability of our Board of Directors to issue preferred stock without stockholder approval, which could be used to institute a poison pill that would work to dilute the stock ownership of a potential hostile acquirer, effectively preventing acquisitions that have not been approved by our Board of Directors;

limitations on the removal of directors; and

advance notice requirements for director nominations and stockholder proposals.

Moreover, because we are incorporated in Delaware, we are governed by the provisions of Section 203 of the Delaware General Corporation Law, which prohibits a person who owns in excess of 15% of our outstanding voting stock from merging or combining with us for a period of three years after the date of the transaction in which the person acquired in excess of 15% of our outstanding voting stock, unless the merger or combination is approved in a prescribed manner.

If you purchase shares of common stock in this offering, you may experience immediate dilution in your investment. You will experience further dilution if we issue additional equity securities in future fundraising transactions.

Purchasers of common stock in this offering may pay a price per share in this offering that exceeds the net tangible book value per share of our common stock. If you purchase shares of our common stock you may experience immediate dilution in the amount of the difference between the price you pay and our as adjusted net tangible book value per share as of December 31, 2013, after giving effect to our January 2014 underwritten public offering, which adjusted net tangible book value per share was \$0.40.

If we issue additional common stock, or securities convertible into or exchangeable or exercisable for common stock, our stockholders may experience additional dilution, and any such issuances may result in downward pressure on the price of our common stock. We also cannot assure you that we will be able to sell shares or other securities in any other offering at a price per share that is equal to or greater 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.

S-25

Table of Contents

SPECIAL NOTE REGARDING FORWARD-LOOKING STATEMENTS

This prospectus supplement, the accompanying prospectus, the documents we have filed with the SEC that are incorporated by reference and any free writing prospectus that we have authorized for use in connection with this offering 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, as amended, 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 include, but are not limited to, statements about:

our business strategy and our expectations with respect to the implementation of our business strategy;

our expectations with respect to the potential therapeutic and commercial value of cabozantinib, cobimetinib and any other of our product candidates;

our expectations with respect to regulatory submissions and approvals and our clinical trials;

our expectations with respect to our intellectual property position; and

our estimates regarding our capital requirements and our need for additional financing.

In some cases, you can identify forward-looking statements by terms such as may, will, should, could, would, plan, anticipate, believe, estimate, project, predict, potential and similar expressions intended to identify forward-looking statements. 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 heading Risk Factors contained in this prospectus supplement, in any free writing prospectuses we may authorize for use in connection with this 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. Thus, you should not assume that our silence over time means that actual events are bearing out as expressed or implied in such forward-looking statements. You should read this prospectus supplement and the accompanying prospectus, together with the documents we have filed with the SEC that are incorporated by reference and any free writing prospectus that we may authorize for use in connection with this offering completely and with the understanding that our actual future results may be materially different from what we expect. We qualify all of the forward-looking statements in the foregoing documents by these cautionary statements.

Table of Contents**USE OF PROCEEDS**

We will not receive any proceeds from the sale of the shares being sold by the selling stockholders.

PRICE RANGE OF OUR COMMON STOCK

Our common stock has traded on the NASDAQ Global Select Market (formerly the NASDAQ National Market) under the symbol EXEL since April 11, 2000. The following table sets forth, for the periods indicated, the high and low intraday sales prices for our common stock as reported by the NASDAQ Global Select Market:

	Common Stock Price	
	High	Low
Fiscal Year Ended December 28, 2012		
Fiscal quarter ended March 30, 2012	\$ 6.57	\$ 4.47
Fiscal quarter ended June 29, 2012	5.59	4.37
Fiscal quarter ending September 28, 2012	6.95	4.19
Fiscal quarter ended December 28, 2012	5.39	4.29
Fiscal Year Ended December 27, 2013		
Fiscal quarter ended March 29, 2013	\$ 5.06	\$ 4.32
Fiscal quarter ended June 28, 2013	5.30	4.33
Fiscal quarter ended September 27, 2013	5.88	4.58
Fiscal quarter ended December 27, 2013	6.14	4.66
Fiscal Year Ending January 2, 2015		
Fiscal quarter ending March 28, 2014 (through February 20, 2014)	\$ 8.41	\$ 5.83

The reported last sale price of our common stock on the NASDAQ Global Select Market on February 20, 2014, was \$7.16 per share. As of February 19, 2014, there were approximately 506 stockholders of record of our common stock.

DIVIDEND POLICY

Since inception, we have not paid dividends on our common stock. We currently intend to retain all future earnings, if any, for use in our business and currently do not plan to pay any cash dividends in the foreseeable future. Any future determination to pay dividends will be at the discretion of our Board of Directors. Our loan and security agreement with Silicon Valley Bank restricts our ability to pay dividends and make distributions. In addition, our note purchase agreement with Deerfield restricts our ability to make distributions.

SELLING STOCKHOLDERS

This prospectus supplement relates to the resale, in one or more offerings, of up to an aggregate of 1,000,000 shares of our common stock that we may issue upon exercise of warrants that we issued to the selling stockholders. The table below provides information about the beneficial ownership of each selling stockholder as to:

the number of shares that are currently, or potentially will be, beneficially held by the selling stockholder (assuming full exercise of the warrants);

the maximum number of shares that may be offered by the selling stockholder under this prospectus supplement; and

the number of shares to be beneficially held by the selling stockholder following the offering (assuming that the maximum number of shares that may be offered by the selling stockholder hereunder are so offered, and no other shares are beneficially acquired by the selling stockholder).

S-27

Table of Contents

We cannot state with certainty the number of shares of our common stock that will be beneficially owned by the selling stockholders after completion of this offering because the selling stockholders may not exercise the warrants and may subsequently acquire the beneficial ownership of other shares of our common stock. Our registration of these shares does not necessarily mean that the selling stockholders will dispose of any or all of the shares.

The information provided in the table below as to number of shares beneficially owned prior to the offering is based on information provided by the selling stockholders. The information provided below is provided as of February 20, 2014, as of which 194,614,305 shares of our common stock were outstanding.

Stockholder	Number of shares beneficially owned prior to the offering (1)(2)	Number of shares offered hereby (1)(2)	Number of shares beneficially owned following the offering
Deerfield Partners, L.P.	449,000	449,000	0
Deerfield International Master Fund, L.P.	551,000	551,000	0

(1) Represents shares of common stock issuable upon exercise of warrants.

(2) James E. Flynn, with an address at 780 Third Avenue, 27th Floor, New York, New York 10017, has voting and dispositive power over these securities.

PLAN OF DISTRIBUTION

The selling stockholders, which, as used herein, includes donees, pledgees, transferees or other successors-in-interest selling shares of our common stock or interests in shares of our common stock received after the date of this prospectus supplement from a selling stockholder as a gift, pledge, partnership distribution or other transfer, may, from time to time, sell, transfer or otherwise dispose of any or all of their shares of our common stock or interests in shares of our common stock on any stock exchange, market or trading facility on which the shares of our common stock are traded or in private transactions. These dispositions may be at fixed prices, at prevailing market prices at the time of sale, at prices related to the prevailing market price, at varying prices determined at the time of sale, or at negotiated prices.

The selling stockholders may use any one or more of the following methods when disposing of shares or interests therein:

ordinary brokerage transactions and transactions in which a broker-dealer solicits purchasers;

block trades in which a broker-dealer will attempt to sell the shares of our common stock as agent, but may position and resell a portion of the block as principal to facilitate the transaction;

purchases by a broker-dealer as principal and resale by the broker-dealer for its account;

an exchange distribution in accordance with the rules of the applicable exchange;

privately negotiated transactions;

short sales effected after the date the registration statement of which this prospectus supplement is a part is filed, and becomes effective, with the Securities and Exchange Commission;

through the writing or settlement of options or other hedging transactions, whether through an options exchange or otherwise;

broker-dealers may agree with the selling stockholders to sell a specified number of shares of our common stock at a stipulated price per share;

a combination of any such methods of sale; and

any other method permitted pursuant to applicable law.

Table of Contents

The selling stockholders may, from time to time, pledge or grant a security interest in some or all of the shares of our common stock owned by them and, if they default in the performance of their secured obligations, the pledgees or secured parties may offer and sell the shares of our common stock, from time to time, under this prospectus supplement and the accompanying prospectus, or under an amendment to this prospectus supplement and/or the accompanying prospectus under Rule 424(b)(3) or other applicable provision of the Securities Act, amending the list of selling stockholders to include the pledgees, transferees or other successors in interest as selling stockholders under this prospectus supplement and the accompanying prospectus. The selling stockholders also may transfer the shares of our common stock in other circumstances, in which case the transferees, pledgees or other successors in interest will be the selling beneficial owners for purposes of this prospectus supplement and the accompanying prospectus.

In connection with the sale of shares of our common stock or interests therein, the selling stockholders may enter into hedging transactions with broker-dealers or other financial institutions, which may in turn engage in short sales of the shares of our common stock in the course of hedging the positions that they assume. The selling stockholders may also sell shares of our common stock short and deliver these securities to close out their short positions, or loan or pledge shares of our common stock to broker-dealers that in turn may sell these securities. The selling stockholders may also enter into option or other transactions with broker-dealers or other financial institutions or create one or more derivative securities which require the delivery to such broker-dealer or other financial institution of shares of our common stock offered by this prospectus supplement and the accompanying prospectus, which shares of our common stock such broker-dealer or other financial institution may resell pursuant to this prospectus supplement and the accompanying prospectus (as supplemented or amended to reflect such transaction).

The aggregate proceeds to the selling stockholders from the sale of shares of our common stock offered by them will be the purchase price of the shares of our common stock less discounts or commissions, if any. Each of the selling stockholders reserves the right to accept and, together with their agents from time to time, to reject, in whole or in part, any proposed purchase of shares of our common stock to be made directly or through agents. We will not receive any of the proceeds from this offering.

The selling stockholders also may resell all or a portion of the shares of our common stock in open market transactions in reliance upon Rule 144 under the Securities Act, provided that they meet the criteria and conform to the requirements of that rule.

The selling stockholders and any underwriters, broker-dealers or agents that participate in the sale of shares of our common stock or interests therein may be underwriters within the meaning of Section 2(11) of the Securities Act. Any discounts, commissions, concessions or profit that they earn on any resale of the shares of our common stock may be underwriting discounts and commissions under the Securities Act. Selling stockholders that are underwriters within the meaning of Section 2(11) of the Securities Act will be subject to any applicable prospectus delivery requirements of the Securities Act.

In order to comply with the securities laws of some states, if applicable, the shares of our common stock may be sold in those jurisdictions only through registered or licensed brokers or dealers. In addition, in some states shares of our common stock may not be sold unless they have been registered or qualified for sale or an exemption from registration or qualification requirements is available and is complied with.

We have advised the selling stockholders that the anti-manipulation rules of Regulation M under the Exchange Act may apply to sales of shares of our common stock in the market and to the activities of the selling stockholders and their affiliates. In addition, we will make copies of this prospectus (as it may be supplemented or amended from time to time) available to the selling stockholders for the purpose of satisfying any applicable prospectus delivery requirements of the Securities Act. The selling stockholders may indemnify any broker-dealer that participates in

transactions involving the sale of the shares of our common stock against certain liabilities, including liabilities arising under the Securities Act.

We have agreed to indemnify the selling stockholders against liabilities, including liabilities under the Securities Act, the Exchange Act and state securities laws, relating to the registration of the shares of our common stock offered under this prospectus.

S-29

Table of Contents

We have agreed with the selling stockholders to keep the registration statement of which this prospectus constitutes a part effective until such time as all of the shares registered hereunder (i) have been sold to the public under a registration statement or pursuant to Rule 144 of the Securities Act, (ii) have been sold, transferred or otherwise disposed of by a selling stockholder in a transaction in which its rights under the registration rights agreement entered into between us and the selling stockholders were not validly assigned, and/or (iii) may be immediately sold to the public without registration or restriction (including without limitation as to volume by each holder thereof) under the Securities Act.

VALIDITY OF COMMON STOCK

Cooley LLP, San Francisco, California, will pass upon the validity of the common stock offered hereby.

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 fiscal year ended December 27, 2013, and the effectiveness of our internal control over financial reporting as of December 27, 2013, as set forth in their reports thereon which are 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 reports, given on their authority as experts in accounting and auditing.

S-30

Table of Contents

Prospectus

Common Stock

From time to time, we may offer and sell shares of common stock in amounts, at prices and on terms described in one or more supplements to this prospectus. Selling shareholders who may be named in a supplement to this prospectus may also from time to time offer and sell our ordinary shares, in one or more offerings.

This prospectus describes some of the general terms that may apply to an offering of our common stock. We will provide the specific terms of these offerings and securities 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 securities being offered.

We may offer and sell shares of common stock to or through one or more underwriters, dealers and agents, or directly to purchasers, on a continuous or delayed basis. Selling shareholders may sell shares from time to time on or off the NASDAQ Global Select Market in regular brokerage transactions, in transactions directly with market makers or in privately negotiated transactions. We will not receive any of the proceeds from the sale of those shares. The supplements to this prospectus will provide the specific terms of the plan of distribution.

If any agents or underwriters are involved in the sale of any securities with respect to which this prospectus is being delivered, the names of such agents or underwriters and any applicable fees, commissions, discounts and over-allotment options will be set forth in a prospectus supplement. The price to the public of such securities and the net proceeds that we or the selling stockholders expect to receive from such sale will also be set forth in a prospectus supplement.

Our common stock is listed on The NASDAQ Global Select Market under the trading symbol EXEL. On February 20, 2014, the last reported sale price of our common stock was \$7.16 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 securities covered by the prospectus supplement.

Investing in our common stock involves a high degree of risk. You should review carefully the risks and uncertainties described under the heading Risk Factors 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 other documents that are incorporated by reference into this prospectus.

This prospectus may not be used to consummate a sale of securities unless accompanied by 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 February 21, 2014.

Table of Contents

TABLE OF CONTENTS

<u>ABOUT THIS PROSPECTUS</u>	i
<u>PROSPECTUS SUMMARY</u>	1
<u>RISK FACTORS</u>	2
<u>SPECIAL NOTE REGARDING FORWARD-LOOKING STATEMENTS</u>	2
<u>USE OF PROCEEDS</u>	3
<u>DESCRIPTION OF CAPITAL STOCK</u>	3
<u>SELLING STOCKHOLDERS</u>	5
<u>PLAN OF DISTRIBUTION</u>	5
<u>LEGAL MATTERS</u>	5
<u>EXPERTS</u>	6
<u>WHERE YOU CAN FIND MORE INFORMATION</u>	6
<u>INCORPORATION OF CERTAIN INFORMATION BY REFERENCE</u>	6

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 SEC, utilizing a shelf registration process. Under this shelf registration process, we or selling stockholders may offer and sell, in one or more offerings, shares of common stock as described in this prospectus. This prospectus provides you with a general description of the shares we may offer.

Each time we or selling stockholders 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 securities being offered.

This prospectus may not be used to consummate a sale of securities 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 different

or additional information. This prospectus is an offer to sell only the securities 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 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 a security. Our business, financial condition, results of operations and prospects may have changed since those dates.

Table of Contents

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 entitled **Where You Can Find More Information**.

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 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 heading **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 and the information incorporated herein by reference include trademarks, service marks and trade names owned by us or other companies. All trademarks, service marks and trade names included or incorporated by reference into this prospectus, any applicable prospectus supplement or any related free writing prospectus are the property of their respective owners.

Table of Contents

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 securities discussed under the heading 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 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.

References in this prospectus to Exelixis, the Company, we, us and our refer to Exelixis, Inc., a Delaware corporation, and its consolidated subsidiaries, if any, unless otherwise specified.

Exelixis, Inc.

Overview

We are a biotechnology company committed to developing small molecule therapies for the treatment of cancer. Our two most advanced assets, COMETRIQ® (cabozantinib), our wholly-owned inhibitor of multiple receptor tyrosine kinases, and cobimetinib (GDC-0973/XL518), a potent, highly selective inhibitor of MEK, which we out-licensed to Genentech, Inc. (a wholly-owned member of the Roche Group), or Genentech, are currently the subject of six ongoing phase 3 pivotal trials. Top-line results from four of these pivotal trials are expected in 2014.

Company Information

We were incorporated in Delaware in November 1994 as Exelixis Pharmaceuticals, Inc., and we changed our name to Exelixis, Inc. in February 2000.

Our corporate address is 210 East Grand Avenue, South San Francisco, CA 94080, and our telephone number is (650) 837-7000. Our website address is www.exelixis.com. Information found on, or accessible through, our website is not a part of, and is not incorporated into, this prospectus, and you should not consider it part of this prospectus or part of any prospectus supplement or free writing prospectus. Our website address is included in this document as an inactive textual reference only.

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 securities offered by us hereunder, if any, for working capital and general corporate purposes, including research and development expenses and capital expenditures. See Use of Proceeds in this prospectus.

Shares of our common stock may be offered by selling stockholders under an applicable prospectus supplement to this prospectus. We will not receive any of the proceeds from the sale or other disposition of shares of our common stock sold by selling stockholders in any offering by them.

The NASDAQ Global Select Market Listing

Our common stock is listed on The NASDAQ Global Select Market under the symbol EXEL. The applicable prospectus supplement will contain information, where applicable, as to other listings, if any, on The NASDAQ Global Select Market or any other securities market or other exchange of the securities covered by the applicable prospectus supplement.

Table of Contents

RISK FACTORS

Investing in our securities involves a high degree of risk. Before deciding whether to invest in our securities, you should consider carefully the risks and uncertainties described under the heading **Risk Factors** contained in the applicable prospectus supplement and any related free writing prospectus, and discussed under the section entitled **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 seriously 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 entitled **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, as amended, 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 include, but are not limited to, statements about:

our business strategy and our expectations with respect to the implementation of our business strategy;

our expectations with respect to the potential therapeutic and commercial value of cabozantinib, cobimetinib and any other of our product candidates;

our expectations with respect to regulatory submissions and approvals and our clinical trials;

our expectations with respect to our intellectual property position; and

our estimates regarding our capital requirements and our need for additional financing.

In some cases, you can identify forward-looking statements by terms such as **may, will, should, could, would, plan, anticipate, believe, estimate, project, predict, potential** and similar expressions intended to identify forward-looking statements. 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 heading 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. Thus, you should not assume that our silence over time means that actual events are bearing out as expressed or implied in such forward-looking statements. 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.

Table of Contents

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 securities offered by us hereunder, if any, for working capital and general corporate purposes, including research and development expenses and capital expenditures.

The amounts and timing of our use of the net proceeds from this offering will depend on a number of factors, such as the timing and progress of our research and development efforts, the timing and progress of any partnering and commercialization efforts, technological advances and the competitive environment for our products. As of the date of this prospectus, we cannot specify with certainty all of the particular uses for the net proceeds to us from the sale of the securities offered by us hereunder. Accordingly, our management will have broad discretion in the timing and application of these proceeds. Pending application of the net proceeds as described above, we intend to temporarily invest the proceeds in short-term, interest-bearing instruments.

Shares of our common stock may be offered by selling stockholders under an applicable prospectus supplement to this prospectus. We will not receive any of the proceeds from the sale or other disposition of shares of our common stock sold by selling stockholders in any offering by them.

DESCRIPTION OF CAPITAL STOCK

Our authorized capital stock consists of 400,000,000 shares of common stock, \$0.001 par value, and 10,000,000 shares of preferred stock, \$0.001 par value. A description of material terms and provisions of our certificate of incorporation and bylaws affecting the rights of holders of our capital stock is set forth below. The description is intended as a summary, and is qualified in its entirety by reference to our certificate of incorporation and the bylaws.

Common stock

Dividend rights. Subject to preferences that may apply to shares of preferred stock outstanding at the time, the holders of outstanding shares of our common stock are entitled to receive dividends out of funds legally available if our board of directors, in its discretion, determines to issue dividends and then only at the times and in the amounts that our board of directors may determine.

Voting rights. Each holder of common stock is entitled to one vote for each share of common stock held on all matters submitted to a vote of stockholders. Our certificate of incorporation does not provide for the right of stockholders to cumulate votes for the election of directors. Our certificate of incorporation establishes a classified board of directors, divided into three classes with staggered three-year terms. Only one class of directors is elected at each annual meeting of our stockholders, with the other classes continuing for the remainder of their respective three-year terms.

No preemptive or similar rights. Our common stock is not entitled to preemptive rights and is not subject to conversion, redemption or sinking fund provisions. 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 any series of our preferred stock that we may designate and issue in the future.

Right to receive liquidation distributions. Upon our dissolution, liquidation or winding-up, the assets legally available for distribution to holders of our common stock are distributable ratably among the holders of our common stock, subject to prior satisfaction of all outstanding debt and liabilities and the preferential rights and payment of liquidation

preferences, if any, on any outstanding shares of our preferred stock.

The rights of the holders of our common stock are subject to, and may be adversely affected by, the rights of holders of shares of any preferred stock that we may designate and issue in the future.

Table of Contents***Preferred stock***

Our board of directors is authorized, subject to limitations prescribed by Delaware law, to issue preferred stock in one or more series, to establish from time to time the number of shares to be included in each series and to fix the designation, powers, preferences and rights of the shares of each series and any of its qualifications, limitations or restrictions. Our board of directors can also increase or decrease the number of shares of any series, but not below the number of shares of that series then outstanding, without any further vote or action by our stockholders. Our board of directors may authorize the issuance of preferred stock with voting or conversion rights that could adversely affect the voting power or other rights of the holders of the common stock. The issuance of preferred stock, while providing flexibility in connection with financings, possible acquisitions and other corporate purposes, could, among other things, have the effect of delaying, deferring, discouraging or preventing a change in control of our company, may adversely affect the market price of our common stock and the voting and other rights of the holders of common stock, and may reduce the likelihood that common stockholders will receive dividend payments and payments upon liquidation.

Outstanding warrants

As of February 20, 2014, we had warrants outstanding to purchase an aggregate of 1,000,000 shares of common stock with an exercise price of \$7.40 per share expiring on June 4, 2014, warrants outstanding to purchase an aggregate of 441,215 shares of common stock with an exercise price of \$6.05 per share expiring on June 10, 2014, and warrants outstanding to purchase an aggregate of 1,000,000 shares of common stock with an exercise price of \$9.70 per share expiring on January 22, 2016, subject to a reset of the exercise price and two-year extension of the term if we exercise an option to extend the maturity date of our indebtedness to the warrant holders.

Anti-takeover effects of provisions of our certificate of incorporation and bylaws and Delaware law

Certificate of incorporation and bylaws. Our certificate of incorporation provides that our board of directors is divided into three classes with staggered three-year terms. Only one class of directors is elected at each annual meeting of our stockholders, with the other classes continuing for the remainder of their respective three-year terms. Because holders of our common stock do not have cumulative voting rights in the election of directors, stockholders holding a majority of the shares of common stock outstanding are able to elect all of the directors to be elected at each annual meeting of our stockholders. Our board of directors is able to elect a director to fill a vacancy created by the expansion of the board of directors or due to the resignation or departure of an existing board member. Our certificate of incorporation and bylaws also provide that all stockholder actions must be effected at a duly called meeting of stockholders and not by a consent in writing, and that only the board of directors pursuant to a resolution adopted by a majority of the total number of authorized directors may call a special meeting of stockholders. In addition, our bylaws include a requirement for the advance notice of nominations for election to the board of directors or for proposing matters that can be acted upon at a stockholders' meeting. Our certificate of incorporation provides for the ability of the board of directors to issue, without stockholder approval, up to 10,000,000 shares of preferred stock with terms set by the board of directors, which rights could be senior to those of our common stock. Our certificate of incorporation and bylaws also provides that approval of at least 66 2/3% of the shares entitled to vote at an election of directors will be required to adopt, amend or repeal our bylaws, or repeal the provisions of our certificate of incorporation regarding the election of directors and the inability of stockholders to take action by written consent in lieu of a meeting.

The foregoing provisions make it difficult for holders of our common stock to replace our board of directors. 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 control of our company.

Table of Contents

Section 203 of the Delaware General Corporation Law

We are subject to the provisions of Section 203 of the Delaware General Corporation Law regulating corporate takeovers. This section prevents some Delaware corporations from engaging, under some circumstances, in a business combination, which includes a merger or sale of at least 10% of the corporation's assets with any interested stockholder, meaning a stockholder who, together with affiliates and associates, owns or, within three years prior to the determination of interested stockholder status, did own 15% or more of the corporation's outstanding voting stock, unless:

the transaction is approved by the board of directors prior to the time that the interested stockholder became an interested stockholder;

upon consummation of the transaction which resulted in the stockholder's becoming an interested stockholder, the interested stockholder owned at least 85% of the voting stock of the corporation outstanding at the time the transaction commenced; or

at or subsequent to such time that the stockholder became an interested stockholder the business combination is approved by the board of directors and authorized at an annual or special meeting of stockholders by at least two-thirds of the outstanding voting stock which is not owned by the interested stockholder.

A Delaware corporation may opt out of these provisions with an express provision in its original certificate of incorporation or an express provision in its certificate of incorporation or bylaws resulting from a stockholders amendment approved by a majority of the outstanding voting shares. We have not opted out of these provisions and do not plan to do so. The statute could prohibit or delay mergers or other takeover or change in control attempts and, accordingly, may discourage attempts to acquire us.

Transfer Agent and Registrar

The transfer agent and registrar for our common stock is Computershare Shareowner Services LLC: 1-877-813-9419.

Listing on The NASDAQ Global Select Market

Our common stock is listed on The NASDAQ Global Select Market under the symbol EXEL. The applicable prospectus supplement will contain information, where applicable, as to any other listing, if any, on The NASDAQ Global Select Market or any securities market or other exchange of the preferred stock covered by such prospectus supplement.

SELLING STOCKHOLDERS

If the registration statement of which this prospectus is a part is used by any selling stockholder for the resale of any shares of our common stock registered thereunder, information about such selling stockholder, its beneficial ownership of our securities and its relationship with us will be set forth in a supplement to this prospectus, or in one or more documents incorporated by reference into this prospectus or the applicable prospectus supplement.

PLAN OF DISTRIBUTION

We may offer and sell shares of our common stock, and any selling stockholders may offer and sell shares of our common stock, in offerings hereunder to or through one or more underwriters, dealers and agents, or directly to purchasers, on a continuous or delayed basis. We will provide the specific plan of distribution for any shares of our common stock to be offered by us or by selling stockholders in a supplement to this prospectus.

LEGAL MATTERS

Unless otherwise indicated in the applicable prospectus supplement, the validity of the securities offered by this prospectus, and any supplement thereto, will be passed upon for us by Cooley LLP, San Francisco, California.

Table of Contents

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 fiscal year ended December 27, 2013, and the effectiveness of our internal control over financial reporting as of December 27, 2013, as set forth in their reports thereon which are 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 reports, given on their authority as experts in accounting and auditing.

WHERE YOU CAN FIND MORE 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. 000-59687):

our Annual Report on Form 10-K for the year ended December 27, 2013, which was filed on February 20, 2014;

the information specifically incorporated by reference into the 2012 Form 10-K from our definitive proxy statement on Schedule 14A which was filed on April 10, 2012;

our Current Reports on Form 8-K filed on January 22, 2014, January 23, 2014, and February 12, 2014; and

the description of our common stock in our registration statement on Form 8-A filed with the SEC on April 6, 2000, including any amendments thereto or reports filed for the purposes of updating this 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, including those made after the date of the filing of the registration statement of which this prospectus is a part, until we file a post-effective amendment that indicates the termination of the offering of the securities 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.

Table of Contents

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

Exelixis, Inc.

210 East Grand Avenue

South San Francisco, CA 94080

(650) 837-7000

Attn: Corporate Secretary