FORM 424B5

Prospectus filed pursuant to Rule 424(b)(5)

Filing Date: **2013-01-15**
SEC Accession No. 0001047469-13-000234

FILER

ONYX PHARMACEUTICALS INC
CIK:**1012140**| IRS No.: **943154463** | State of Incorp.:**DE** | Fiscal Year End: **1231**
Type: **424B5** | Act: **33** | File No.: **333-186046** | Film No.: **13531109**
SIC: **2836** Biological products, (no disgnostic substances)

Mailing Address
249 E. GRAND AVE.
SOUTH SAN FRANCISCO CA
94080

Business Address
249 E. GRAND AVE.
SOUTH SAN FRANCISCO CA
94080
650-266-0000

Filed Pursuant to Rule 424(b)(5)
Registration Statement No. 333-186046

The information in this preliminary prospectus supplement and the accompanying prospectus is not complete and may be changed. This preliminary prospectus supplement and the accompanying prospectus are not an offer to sell these securities and are not soliciting an offer to buy these securities in any jurisdiction where the offer or sale is not permitted.

Subject to Completion January 15, 2013

Prospectus Supplement to Prospectus Dated January 15, 2013

Shares

Common Stock

We are offering shares of our common stock to be sold in this offering.

Our common stock is quoted on The NASDAQ Global Select Market under the symbol "ONXX." On January 14, 2013, the reported last sale price of our common stock on The NASDAQ Global Select Market was $82.82 per share.

See "Risk Factors" on page S-6 to read about factors you should consider before buying shares of the common stock.

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

	Per Share	Total
Public offering price	$	$
Underwriting discount	$	$
Proceeds, before expenses, to us	$	$

To the extent that the underwriters sell more than shares of common stock, the underwriters have the option to purchase up to an additional shares from us at the initial price to public less the underwriting discount.

The underwriters expect to deliver the shares against payment in New York, New York on January , 2013.

BofA Merrill Lynch **Barclays**

Prospectus Supplement dated January , 2013.

TABLE OF CONTENTS

Prospectus Supplement

Prospectus

No dealer, salesperson or other person is authorized to give any information or to represent anything not contained in this prospectus supplement or the accompanying prospectus. You must not rely on any unauthorized information or representations. This prospectus supplement and the accompanying prospectus is an offer to sell only the shares offered hereby, but only under circumstances and in jurisdictions where it is lawful to do so. The information contained in this prospectus supplement and the accompanying prospectus is current only as of their respective dates.

ABOUT THIS PROSPECTUS SUPPLEMENT

This document consists of two parts. The first part is this prospectus supplement, which describes the specific terms of this offering and also adds to and updates the information contained in the accompanying prospectus and the documents incorporated by reference into this prospectus supplement and the accompanying prospectus. The second part, the accompanying prospectus, gives more general information, some of which may not apply to this offering. If there is a difference between the information contained in this prospectus supplement, on the one hand, and the information contained in the accompanying prospectus or any document incorporated by reference, on the other hand, you should rely on the information in this prospectus supplement. Generally, when we refer to the prospectus, we are referring to this prospectus supplement and the accompanying prospectus combined.

We have not, and the underwriters have not, authorized anyone else to provide you with information that is in addition to or different from that contained or incorporated by reference in this prospectus supplement and the accompanying prospectus, along with the information contained in any permitted free writing prospectuses we have authorized for use in connection with this offering. We take, and the underwriters take, no responsibility for, and can provide no assurance as to the reliability of, any other information that others may give you. We are offering to sell, and seeking offers to buy, shares of our common stock only in jurisdictions where offers and sales are permitted. The information contained in this prospectus supplement, the accompanying prospectus and any authorized free writing prospectus is accurate only as of the date of this prospectus supplement or the date of the accompanying prospectus, and the information in the documents incorporated by reference in this prospectus supplement and the accompanying prospectus is accurate only as of the date of those respective documents, regardless of the time of delivery of this prospectus supplement and the accompanying prospectus or of any sale of shares of our common stock. Our business, financial condition, results of operations and prospects may have changed since those dates. It is important for you to read and consider all information contained or incorporated by reference in this prospectus supplement and the accompanying prospectus in making your investment decision. You should read both this prospectus supplement and the accompanying prospectus, as well as the documents incorporated by reference into this prospectus supplement and the accompanying prospectus, any authorized free writing prospectus, and the additional information described under "Where You Can Find More Information" in this prospectus supplement and in the accompanying prospectus, before investing in our common stock.

Unless stated otherwise, references in this prospectus supplement and the accompanying prospectus to "Onyx," "we," "us," "our" or "the company" refer to Onyx Pharmaceuticals, Inc., a Delaware corporation, and its subsidiaries.

This prospectus supplement and the accompanying prospectus, including the information incorporated by reference into this prospectus supplement and the accompanying prospectus, and any free writing prospectuses we have authorized for use in connection with this offering, include trademarks, service marks and trade names owned by us or others companies. All trademarks, service marks and trade names included or incorporated by reference into this prospectus supplement and the accompanying prospectus, and any free writing prospectuses we have authorized for use in connection with this offering, are the property of their respective owners.

WHERE YOU CAN FIND MORE INFORMATION

We file annual, quarterly and current reports, proxy statements and other information with the Securities and Exchange Commission, or the SEC. You may 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 more information about the operation of the public reference room. The SEC maintains an Internet site that contains reports, proxy and information statements and other information regarding issuers that file electronically with the SEC, including us. The SEC's Internet site can be found at *http://www.sec.gov*.

INCORPORATION OF CERTAIN INFORMATION BY REFERENCE

The SEC allows us to incorporate by reference the information we file with it, which means that we can disclose important information to you by referring you to another document that we have filed separately with the SEC. You should read the information incorporated by reference because it is an important part of this prospectus supplement and the accompanying prospectus. We incorporate by reference the following information or documents that we have filed with the SEC (Commission File No. 0-28298):

our annual report on Form 10-K for the fiscal year ended December 31, 2011, or the Annual Report;

the information specifically incorporated by reference into our Annual Report from our definitive proxy statement on Schedule 14A, filed with the SEC on April 2, 2012;

our quarterly reports on Form 10-Q for the quarters ended March 31, 2012, June 30, 2012 and September 30, 2012;

our current reports on Form 8-K (other than information furnished rather than filed) filed with the SEC on February 8, 2012, February 16, 2012, May 22, 2012, July 20, 2012, and September 27, 2012; and

the description of our common stock set forth in our registration statement on Form 8-A, filed with the SEC on April 2, 1996, including any amendments or reports filed for the purposes of updating this description.

Any information in any of the foregoing documents will automatically be deemed to be modified or superseded to the extent that information in this prospectus or in a later filed document that is incorporated or deemed to be incorporated herein by reference modifies or replaces such information.

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) made with the SEC pursuant to Sections 13(a), 13(c), 14 or 15(d) of the Securities Exchange Act of 1934, as amended, or the Exchange Act, until we file a post-effective amendment which indicates the termination of the offering of the securities made by this prospectus supplement and the accompanying prospectus. Information in such future filings updates and supplements the information provided in this prospectus supplement and the accompanying 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.

We will provide to each person, including any beneficial owner, to whom this prospectus supplement and the accompanying prospectus is delivered, without charge upon written or oral request, a copy of any or all of the documents that are incorporated by reference herein, including exhibits which are specifically incorporated by reference into such documents. Requests should be made to us by mail care of Investor Relations, in care of: Onyx Pharmaceuticals, Inc., 249 E. Grand Avenue, South San Francisco, CA 94080, or by telephone by calling (650) 266-0000.

Table of Contents

FORWARD-LOOKING STATEMENTS

This prospectus supplement, the accompanying prospectus, the documents that we have filed with the SEC that are incorporated by reference in this accompanying prospectus and any authorized free writing prospectus contain forward-looking statements within the meaning of Section 27A of the Securities Act of 1933, as amended, or the Securities Act, and within the meaning of Section 21E of the Exchange Act that are subject to the "safe harbor" created by those sections. These forward-looking statements can generally be identified as such because the context of the statement will include words such as "may," "will," "expect," "anticipate," "intend," "believe," "hope," "assume," "estimate," "plan," "future," "potential," "likely," "unlikely," "opportunity," "predict," "continue," "should," or the negative of these terms and similar expressions intended to identify forward-looking statements. Discussions containing these forward-looking statements may be found, among other places, in "Business" and in "Management's Discussion and Analysis of Financial Condition and Results of Operations" incorporated by reference from our most recent annual report on Form 10-K and from our quarterly reports on Form 10-Q for the quarterly periods ended subsequent to our filing of such annual report on Form 10-K, as well as any amendments thereto reflected in subsequent filings with the SEC. These forward-looking statements include but are not limited to statements about:

- our strategy;
- the progress, timing and results of our development programs, including clinical testing;
- sufficiency of our cash resources;
- revenues from existing and new collaborations;
- product development;
- our research and development and other expenses; and
- our operations and legal risks.

These forward-looking statements are based largely on our expectations and projections about future events and future trends affecting our business, and are subject to risks and uncertainties that could cause actual results to differ materially form those anticipated in the forward-looking statements. Before deciding to purchase our common stock, you should carefully consider the risk factors described in the "Risk Factors" section of this prospectus supplement, in addition to the other information set forth in this prospectus supplement, the accompanying prospectus, any authorized free writing prospectus and the documents incorporated by reference herein and therein.

In addition, past financial and/or operating performance is not necessarily a reliable indicator of future performance and you should not use our historical performance to anticipate results or future period trends. We can give no assurances that any of the events anticipated by the forward-looking statements will occur or, if any of them do, what impact they will have on our results of operations and financial condition.

Except as required by law, we undertake no obligation to publicly revise our forward-looking statements to reflect events or circumstances that arise after the filing of this prospectus supplement or any authorized free writing prospectus, or documents incorporated by reference herein and therein, that include forward-looking statements.

Table of Contents

SUMMARY

This summary highlights selected information appearing elsewhere or incorporated by reference in this prospectus supplement and the accompanying prospectus, and may not contain all of the information that is important to you in making your investment decision. This prospectus supplement and the accompanying prospectus include information about the shares of common stock that we are offering as well as information regarding our business. You should read this prospectus supplement and the accompanying prospectus, including the information incorporated by reference and any free writing prospectus that we have authorized for use in connection with this offering, in their entirety. You should carefully consider the information set forth under "Risk Factors" beginning on page S-6 of this prospectus supplement before making your investment decision.

Onyx Pharmaceuticals, Inc.

Overview

We are a biopharmaceutical company dedicated to developing innovative therapies that target the molecular mechanisms that cause cancer. By applying our expertise to develop and commercialize therapies designed to exploit the genetic and molecular differences between cancer cells and normal cells, we have built two franchise platforms−one in kinase inhibition and one in proteasome inhibition. In our kinase inhibitor franchise, our lead product, Nexavar® (sorafenib) tablets, is approved for unresectable liver cancer and advanced kidney cancer. With our development and marketing partner Bayer HealthCare Pharmaceuticals Inc., or Bayer, we share equally in the profits and losses of Nexavar worldwide, except Japan. A second oral multikinase inhibitor, Stivarga® (regorafenib) tablets, a Bayer compound, is approved in the United States for the treatment of metastatic colorectal cancer; and Bayer also submitted a supplemental New Drug Application, or sNDA, in the United States, for regorafenib for the treatment of gastrointestinal stromal tumors, or GIST, in patients whose disease has progressed despite prior treatment. Onyx receives a twenty percent royalty on global net sales of Stivarga in oncology.

In our proteasome inhibitor franchise, Kyprolis™ (carfilzomib) for Injection is approved in the United States for the treatment of patients with multiple myeloma who have received at least two prior therapies, including bortezomib and an immunomodulatory agent (IMiD), and have demonstrated disease progression on or within 60 days of completion of the last therapy. We are also developing two other novel proteasome inhibitors, including an oral proteasome inhibitor oprozomib (ONX 0912) and an immunoproteasome inhibitor (ONX 0914). In addition, we expect to continue to expand our development pipeline, with multiple clinical or preclinical stage product candidates.

Our Strategy

We plan to achieve our business strategy of transforming Onyx into a leading biopharmaceutical company in the oncology market by:

- establishing Kyprolis as a treatment for relapsed and refractory multiple myeloma;
- investing broadly in clinical testing to evaluate Kyprolis for additional lines of treatment for multiple myeloma;
- maximizing current opportunities worldwide for Kyprolis in approved indications;
- establishing Bayer's Stivarga as a treatment for metastatic colorectal cancer and potentially for other indications;
- investing with our partner Bayer in a development program for Nexavar by pursuing other types of cancer, including thyroid and breast cancer;

preparing for future commercialization opportunities of Nexavar, Stivarga, Kyprolis and oprozomib; and

continuing to expand our pipeline by advancing earlier stage therapies, as well as pursuing other opportunities using a disciplined financial approach.

Business Highlights

Proteasome Inhibitor Franchise

On July 20, 2012, we received accelerated approval of Kyprolis™ for injection, a proteasome inhibitor, indicated for the treatment of patients with multiple myeloma who have received at least two prior therapies, including bortezomib and an immunomodulatory agent (IMiD), and have demonstrated disease progression on or within 60 days of completion of the last therapy. Approval was based on response rate. Clinical benefit, such as improvement in survival or symptoms, has not been verified. Since the launch of Kyprolis in late July 2012, net sales have exceeded $62 million for the fiscal year ended December 31, 2012. Through October 2012, approximately 25% of the estimated 10,000 to 15,000 patients living with third-line or later multiple myeloma in the U.S. annually have received Kyprolis.

On July 2, 2012, we announced that we have begun enrollment in the ENDEAVOR trial, a Phase 3 trial evaluating Kyprolis in combination with dexamethasone, versus Velcade® (bortezomib) with dexamethasone, in patients with relapsed multiple myeloma.

Kinase Inhibitor Franchise

On January 3, 2013, Onyx and Bayer announced top-line results from the DECISION trial which evaluated Nexavar tablets for the treatment of patients with locally advanced or metastatic radioactive iodine (RAI)-refractory differentiated thyroid cancer. The study met its primary endpoint of improving progression-free survival. Full results are expected to be presented at an upcoming medical meeting. Onyx and Bayer anticipate that this data will form the basis for regulatory submissions of Nexavar in the treatment of RAI-refractory differentiated thyroid cancer.

On September 27, 2012, we announced that Bayer received accelerated approval in the United States of Stivarga® (regorafenib) tablets, the oral multikinase inhibitor, indicated for the treatment of metastatic colorectal cancer (mCRC) in patients whose disease has progressed despite prior treatment (including fluoropyrimidine-, oxaliplatin-, and irinotecan-based chemotherapy, an anti-VEGF therapy, and, if KRAS wild type, an anti-EGFR therapy). Bayer has also submitted applications in Europe and Japan seeking marketing authorization for Stivarga for the treatment of patients with mCRC, and the application in Japan has received priority review designation. The United States approval was based on improvement in overall survival and progression-free survival compared to placebo in patients with mCRC whose disease had progressed after approved standard therapies. Onyx co-promotes Stivarga in the United States with Bayer, and receives a twenty percent royalty on global net sales of Stivarga in oncology.

On August 30, 2012, Bayer announced the submission of a supplemental New Drug Application, or sNDA, to the U.S. Food and Drug Administration, or FDA, for regorafenib for the treatment of metastatic unresectable gastrointestinal stromal tumors (GIST) in patients whose disease had progressed despite prior treatment. The submission is based on data from the pivotal Phase 3 GRID (**G**IST−**R**egorafenib **I**n Progressive **D**isease) trial, which showed that regorafenib plus best supportive care (BSC) significantly improved progression-free survival (PFS) compared to placebo plus BSC in patients with metastatic and/or unresectable GIST who were previously treated with imatinib and sunitinib. In October 2012, the U.S. FDA granted priority review to Bayer's sNDA.

On December 21, 2012, Bayer announced that Bayer Yakuhin Ltd., a Bayer subsidiary, had submitted a marketing authorization application for regorafenib for the treatment of GIST to the Ministry of Health, Labour and Welfare (MHLW) in Japan.

In October 2011, we restructured our partnership with Bayer for the global development and marketing of Nexavar and entered into a new agreement related to regorafenib. Under the terms of the agreements, regorafenib is a Bayer compound, and Bayer will have the final decision-making authority for global development and commercialization.

On July 23, 2012, Bayer, Onyx, and Astellas Pharma Inc. announced that the Phase 3 SEARCH (**S**orafenib and **E**rlotinib, a r**A**ndomized t**R**ial proto**C**ol for the treatment of patients with **H**epatocellular carcinoma) trial evaluating the efficacy and safety of the addition of Tarceva® (erlotinib) tablets to Nexavar® (sorafenib) tablets did not improve overall survival for patients with unresectable hepatocellular carcinoma (HCC) compared to treatment with Nexavar alone.

Cash, cash equivalents and current and non-current marketable securities at September 30, 2012 were $573.0 million, a decrease of $95.4 million, or 14%, from $668.4 million at December 31, 2011. The decrease is primarily attributable to net cash used in operations and the increase in research and development expenses for the development of Kyprolis.

Corporate Information

We were incorporated in California in February 1992 and reincorporated in Delaware in May 1996. Our principal office is located at 249 E. Grand Avenue, South San Francisco, CA 94080 and our telephone number is +1 (650) 266-0000. Our website is located at www.onyx.com. Our website address is included in this document only as a reference. Information found on, or accessible through, our website is not a part of, and not incorporated into, this prospectus supplement or the accompanying prospectus.

THE OFFERING

Common Stock offered by Onyx	shares
Option to purchase additional shares	We have granted the underwriters an option to purchase up to shares of our common stock
Common Stock to be outstanding after the offering	shares (or shares if the underwriters' option to purchase additional shares is exercised in full)
Use of Proceeds	We intend to use the net proceeds from this offering to fund our clinical development program for carfilzomib and oprozomib, and for other research and development activities, both ongoing and planned, as well as sales and marketing activities to commercialize Kyprolis around the world, and for general corporate purposes, including working capital. We may also use a portion of our net proceeds from these offerings to make potential milestone payments to the Proteolix, Inc., or Proteolix, shareholders; to pay a portion of or all of our $230 million convertible debt when due; to further build and diversify our pipeline by in-licensing products or product candidates or investing in or acquiring businesses or technologies that we believe are complementary to our own. We have no current commitments or agreements with respect to any such transactions. We have not determined the amounts we plan to spend on any of the areas listed above or the timing of these expenditures. As a result, our management will have broad discretion to allocate the net proceeds of these offerings. Pending the application of the net proceeds from these offerings, we expect to invest the proceeds in investment-grade, interest-bearing securities. See the section entitled "Use of Proceeds," below.
Risk Factors	See "Risk Factors" beginning on page S-6 for a discussion of factors you should consider carefully before making an investment decision.
NASDAQ Global Select Market Symbol for our Common Stock	ONXX

The number of shares of our common stock to be outstanding after the offering is based on 67,444,506 shares of our common stock outstanding as of December 31, 2012 and excludes as of that date:

6,408,515 shares of common stock issuable upon exercise of outstanding stock options with a weighted average exercise price of approximately $31.34 per share;

3,161,015 shares of common stock available for future award under our stock option plans;

154,856 shares of common stock available for sale under our employee stock purchase plan;

469,923 shares of restricted common stock issued under stock bonus awards; and

5,800,761 shares of common stock reserved for issuance upon conversion of 4.0% convertible senior notes due 2016 with an aggregate principal amount of $230.0 million.

Unless otherwise stated, all information contained in this prospectus supplement:

assumes no exercise of the underwriters' option; and

reflects all currency amounts in United States dollars.

RISK FACTORS

You should carefully consider the risks described below, together with all of the other information included in this prospectus supplement, the accompanying prospectus and documents incorporated by reference herein, in considering our business and prospects. The risks and uncertainties described below contain forward-looking statements, and our actual results may differ materially from those discussed here. Additional risks and uncertainties not presently known to us or that we currently deem immaterial also may impair our business operations. Each of these risk factors could adversely affect our business, operating results and financial condition, as well as adversely affect the value of an investment in our common stock.

Management will have broad discretion as to the use of the proceeds from this offering, and we may not use the proceeds effectively.

We have not designated the amount of net proceeds from this offering that we will use for any particular purpose. Accordingly, our management will have broad discretion as to the application of the net proceeds and could use them for purposes other than those contemplated at the time of this offering. See the section entitled "Use of Proceeds," below. Our stockholders may not agree with the manner in which our management chooses to allocate and spend the net proceeds. Moreover, our management may use the net proceeds for corporate purposes that may not increase our profitability or market value.

Future sales or the possibility of future sales of a substantial amount of our common stock may depress our stock price.

In connection with this offering, we are restricted from issuing additional shares of common stock, subject to specified exceptions, for a period of 60 days from the date of this prospectus supplement. Our directors and executive officers have agreed not to sell or otherwise dispose of any of their shares, subject to specified exceptions, for a period of 60 days from the date of this prospectus supplement. Exceptions to these lock-up agreements are described under "Underwriting." Sales of substantial amounts of our common stock after this offering, or the perception that we may issue substantial amounts of common stock, may adversely affect the price of our common stock and impair our ability to raise capital through the sale of additional equity securities. We cannot predict the effect that future sales of our common stock, convertible notes or other equity-linked securities would have on the market price of our common stock. The price of our common stock could be affected by possible sales of our common stock by investors who view our convertible notes or other equity-linked securities as more attractive means of equity participation in our company than our common stock, and by hedging or arbitrage trading activity which we expect to occur involving our common stock. This hedging or arbitrage could, in turn, affect the market price of our common stock.

Conversion of our convertible senior notes due 2016 will dilute the ownership interests of existing stockholders.

If and to the extent that we deliver shares of our common stock in settlement of our conversion obligation with respect to any of our outstanding 4.0% convertible senior notes due 2016, or the 2016 notes, the ownership interests of our existing stockholders will be diluted. Any sales in the public market of our common stock issuable upon such conversion could adversely affect prevailing market prices of our common stock. In addition, the existence of the 2016 notes may encourage short-selling by holders of the 2016 notes engaged in hedging or arbitrage, and by other market participants.

Nexavar® is currently our main source of commercial revenues. If Nexavar fails and we, independently or in collaboration with Bayer, are unable to successfully commercialize other products, our business would fail.

Nexavar generated substantially all our commercial revenues for the quarter and nine months ended September 30, 2012, and we rely on these revenues to fund our operations. Unless we can

successfully commercialize Kyprolis and other product candidates and/or unless Bayer successfully commercializes Stivarga, we will continue to rely on Nexavar to generate most of our revenues and fund our operations. Kyprolis received FDA approval in July 2012 and is in the early stages of commercialization, while our other product candidates are still development-stage and/or subject to regulatory review, and we may never obtain approval of or earn revenues from any of our product candidates. Similarly, Stivarga received FDA approval in September 2012 but we and Bayer may be unsuccessful in commercializing it. Successful development and commercialization of these compounds and our other product candidates is highly uncertain and depends on a number of factors, many of which are beyond our control.

We have never marketed a drug without a partner before, and we may not be able to commercialize Kyprolis successfully.

In order to successfully commercialize Kyprolis, we have expanded our U.S. sales force. If we obtain marketing approval outside the United States, we may develop and maintain an international sales, marketing and distribution infrastructure, which may be difficult and time consuming, and may require substantial financial and other resources. We have limited experience building and maintaining a commercialization infrastructure in the United States and no experience in building such an infrastructure internationally. Factors that may hinder our efforts to maintain our expanded U.S. presence and develop an international sales, marketing, and distribution infrastructure include:

- inability to recruit, retain and effectively manage adequate numbers of effective sales and marketing personnel;
- inability to establish or maintain relationships with wholesalers and distributors;
- inability of sales personnel to obtain access to or convince adequate numbers of physicians to prescribe our products;
- lack of complementary products to be offered by sales personnel, which may put us at a competitive disadvantage relative to companies with more extensive product lines; and
- unforeseen delays, costs and expenses associated with creating international capabilities, including an international sales and marketing organization and international supply chain and reimbursement capabilities.

If we are unable to sustain our sales force and marketing capability for Kyprolis, it will reduce our ability to generate product revenue, may generate increased expenses and Kyprolis may never become profitable.

We will need to continue to expend significant time and resources to train our Kyprolis sales force to be credible, persuasive and compliant in discussing Kyprolis with the specialists treating the patients indicated under label. We will also need to continue to train our sales force to ensure that a consistent and appropriate message about Kyprolis is being delivered to our potential customers. In addition, if we are unable to effectively train our sales force and equip them with effective materials, including medical and sales literature to help them inform and educate potential customers about the benefits and risks of Kyprolis and its proper administration, our ability to successfully commercialize Kyprolis could be diminished, which could have a material adverse effect on our financial condition, stock price and operations.

We may also maintain high inventory levels to mitigate risks such as variability in product demand, long lead times for manufacturing, supply interruptions of raw materials and production disruptions at our approved manufacturing sites due to contamination, equipment failure or other facility-related issues. The capital required to maintain our desired inventory levels may impact our liquidity and cash flows, and may also heighten the risk of inventory obsolescence and write-offs.

Our stock price is volatile, our operating results are unpredictable, we have a history of losses and we may be unable to achieve and sustain profitability.

Our stock price is volatile and is likely to continue to be volatile. A variety of factors may have a significant effect on our stock price, including:

- fluctuations in our results of operations, including sales of Nexavar, Stivarga and Kyprolis;
- results from or speculation about clinical trials or the regulatory status of Nexavar, Kyprolis, Stivarga or other product candidates;
- decisions or changes in policy by regulatory agencies, or changes in regulatory requirements;
- announcements by us regarding, or speculation about, our strategic transactions or business development activities;
- ability to accrue patients into clinical trials or submit or obtain approval of regulatory filings;
- developments in our relationship with Bayer, Ono Pharmaceutical Co., Ltd. and other commercialization partners;
- developments in our relationship with, or other problems at, our contract manufacturing organizations, and problems in our supply chain systems, including recalls, quality problems and stockouts and other similar problems;
- changes in healthcare reimbursement policies or other government regulations;
- changes in generally accepted accounting principles and changes in tax laws;
- announcements by us or our competitors of innovations, clinical data results, new products or new regulatory filings;
- sales by us of our common stock or debt securities; and
- foreign currency fluctuations, which would affect our share of collaboration profits or losses and net income and expense related to international clinical and commercial operations.

In the past, following our announcement of the accelerated approval of Kyprolis or Bayer's announcements regarding lower than anticipated Nexavar sales and Nexavar clinical trial results, and following our announcements about various clinical and regulatory developments for Kyprolis, our stock price has fluctuated, in some cases significantly.

Our operating results and sales of Nexavar, Kyprolis and Stivarga will likely fluctuate from quarter to quarter and from year to year, and are difficult to predict. Our operating expenses are dependent in part on expenses incurred by Bayer and in certain regions are

independent of Nexavar sales. We have to date incurred losses principally from costs incurred in our research and development programs, from our general and administrative costs and the development of our commercialization infrastructure. We will incur operating losses in the future as we expand our development and commercial activities for Kyprolis and our product candidates. We expect to incur significant operating expenses associated with the development and commercialization of Kyprolis and additional products, including potentially Stivarga, if we elect to conduct separate development of Stivarga in certain indications, at our own expense, as permitted under the regorafenib agreement.

As a result of the acquisition of Proteolix, we may be required to pay up to an additional $365.0 million in three earn-out payments upon the receipt of certain regulatory approvals within pre-specified timeframes. We recorded a liability for this contingent consideration for the three earn-out payments with a fair value of $146.2 million at September 30, 2012 based upon a discounted cash flow model that uses significant estimates and assumptions. Any changes to these estimates and assumptions could significantly impact the fair values recorded for this liability resulting in significant

charges to our Condensed Consolidated Statements of Operations. Moreover, we may, at our discretion, make any of the remaining earn-out payments in the form of cash, shares of Onyx common stock or a combination thereof. If we elect to issue shares of our common stock in lieu of making an earn-out payment in cash, this would have a dilutive effect on our common stock and could cause the trading price of our common stock to decline.

It is difficult for us to accurately forecast profits or losses. It is possible that in some quarters our operating results could disappoint securities analysts or investors. Many factors, including, but not limited to disappointing operating results and/or the other factors outlined above, could cause the trading price of our common stock to decline, perhaps substantially.

We face intense competition and many of our competitors have substantially greater experience and resources than we have.

We are engaged in a rapidly changing and highly competitive field. We are seeking to develop and market oncology products that face significant competition from other products and therapies that currently exist or are being developed.

Nexavar faces significant competition. There are many existing approaches used in the treatment of unresectable liver cancer including alcohol injection, radiofrequency ablation, chemoembolization, cryoablation and radiation therapy. Several other therapies are in development. If Nexavar is unable to compete or be combined successfully with existing approaches or if new therapies are developed for unresectable liver cancer, our business would be harmed.

Similarly, there are several competing therapies approved for the treatment of advanced kidney cancer, including Sutent, a multiple kinase inhibitor marketed in the United States, the European Union and other countries by Pfizer; Torisel, an mTOR inhibitor marketed in the United States, the European Union and other countries by Wyeth; Avastin, an angiogenesis inhibitor approved for the treatment of advanced kidney cancer in the United States and the European Union and marketed by Genentech, a member of the Roche Group; Afinitor, an mTOR inhibitor marketed in the United States and the European Union by Novartis; GlaxoSmithKline's Votrient, a multiple kinase inhibitor, and Pfizer's Inlyta, a kinase inhibitor recently approved by the FDA for the treatment of advanced kidney cancer in the United States. Nexavar's market share in advanced kidney cancer has declined following the introduction of these products into the market. We expect competition to increase as generic versions of competing products are introduced and/or additional new products are approved.

Beyond unresectable liver cancer and advanced kidney cancer, competitors that target the same tumor types as our Nexavar program and that have commercial products or product candidates at various stages of clinical development include Pfizer, Roche, Wyeth, Novartis International AG, Amgen, AstraZeneca PLC, Astellas Pharma Inc., GlaxoSmithKline, Eli Lilly and several others. A number of companies have agents such as small molecules or antibodies targeting VEGF, VEGF receptors, Epidermal Growth Factor, or EGF, EGF receptors, and other enzymes. In addition, many other pharmaceutical companies are developing novel cancer therapies that, if successful, would also provide competition for Nexavar.

A demonstrated survival benefit is often an important element in determining standard of care in oncology. We did not demonstrate a statistically significant overall survival benefit for patients treated with Nexavar in our Phase 3 kidney cancer trial, which we believe was due in part to the crossover of patients from placebo to Nexavar during the conduct of our pivotal clinical trial. Competitors with statistically significant overall survival data could be preferred in the marketplace. The FDA approval of Nexavar permits Nexavar to be marketed as an initial, or first-line, therapy and subsequent lines of therapy for the treatment of advanced kidney cancer, but approvals in some other regions do not. For example, the European Union approval indicates Nexavar only for advanced kidney cancer patients that have failed prior cytokine therapy or whose physicians deem alternate therapies inappropriate. We may be unable to compete effectively against products with broader or different marketing authorizations in one or more countries.

Nexavar may face challenges and competition from generic products. Generic manufacturers may file Abbreviated New Drug Applications, or ANDAs, in the United States seeking FDA authorization to manufacture and market generic versions of Nexavar, together with Paragraph IV certifications that challenge the scope, validity or enforceability of the Nexavar patents. If Bayer and we are unsuccessful at challenging an ANDA the ANDA filer may be able to launch a generic version of Nexavar, which would harm our business. Bayer and we may also be unable to successfully enforce and defend the Nexavar patents and we may face generic competition prior to expiration of the Nexavar patents in 2020.

Similarly, outside the United States, generic drug manufacturers or other competitors may challenge the scope, validity or enforceability of the Nexavar patents, requiring Bayer and us to engage in complex, lengthy and costly litigation or other proceedings. Bayer may be unsuccessful in defending or enforcing the Nexavar patents in one or more countries and could face generic competition prior to expiration of the Nexavar patents, which would harm our business. Generic drug manufacturers may develop, seek approval for, and launch generic versions of Nexavar. For example, a generic version of Nexavar has been launched in Peru and Cipla recently received approval to launch its version of Nexavar in India at a price that is significantly less than that charged for Nexavar in India. Recently, India's controller general of patents, designs and trademarks has granted a compulsory license to the Indian generics drug maker, Natco, to make generic Nexavar. The license does not grant Natco the right to sell Nexavar outside of India. Bayer has appealed the ruling.

Prior to regulatory approval of Kyprolis, we had not marketed products for any hematological cancer, including multiple myeloma, and may be at a disadvantage to our competitors. Kyprolis may face significant competition. Kyprolis competes with products marketed by Millennium Pharmaceuticals, Inc., a wholly owned subsidiary of Takeda Pharmaceutical Company Limited, Celgene Corporation and potentially against agents currently in development for treatment of this disease by Merck & Co. Inc., Bristol-Myers Squibb, Keryx Biopharmaceuticals, Inc., Nereus Pharmaceuticals, Teva Pharmaceutical Industries Ltd., and other companies. Our competitors may develop and commercialize therapies that change the treatment paradigm for multiple myeloma. For example, Millennium is developing a multiple myeloma therapy to be administered orally and Celgene filed its NDA for pomalidomide that has a PDUFA date of February 10, 2013. Pomalidomide could be approved by the FDA with a similar label to Kyprolis in terms of eligible patient population. This could result in Kyprolis being used in later lines due to convenience of pomalidomide oral administration, which could erode new patient share growth and negatively impact Kyprolis sales. Kyprolis, which is administered intravenously, may not compete effectively with orally administered drugs, and we may not succeed in developing an orally administered therapy, which would harm our business.

Stivarga may face significant competition. Bayer has presented positive Stivarga data in CRC third line plus and has reported positive GIST third line plus data. CRC is a competitive marketplace with three approved targeted therapies, one targeted therapy in registration and multiple therapies in phase three development. There are currently no approved therapies in the third line plus setting. GIST is a relatively infrequently occurring tumor for which there are currently two therapies approved in adjuvant, first and second line GIST, but none approved in the third line plus setting.

Bayer and Onyx have disclosed that Stivarga met the primary endpoint in the phase 3 third line plus GRID study in gastrointestinal stromal tumor, or GIST. There are currently two agents approved in adjuvant, first and second line GIST, but none approved in the third line plus setting. Imatinib, marketed by Novartis, is a c-kit inhibitor approved in patients with Kit (CD117) positive unresectable and/or metastatic malignant GIST as well as the adjuvant treatment of adult patients following resection of Kit (CD117) positive GIST. Sunitinib, marketed by Pfizer, is a multi tyrosine kinase inhibitor approved in GIST after disease progression on or intolerance to imatinib. There are several therapies being developed in GIST, most notably phase 3 agents mastinib, by AB Science, and nilotinib by Novartis, and phase 2 agents ganetespib, by Synta, and pazopanib by GlaxoSmithKline.

Many of our competitors, either alone or together with collaborators, have substantially greater financial resources and research and development staffs. In addition, many of these competitors, either alone or together with their collaborators, have significantly greater experience and resources available than us to:

- discover and patent products;
- undertake preclinical testing and human clinical trials;
- seek and obtain FDA and other regulatory approvals;
- manufacture products; and
- market and obtain reimbursement for products.

Accordingly, our competitors may be more successful than we in any or all of these areas. Developments by competitors may render our product candidates obsolete or noncompetitive. We face and will continue to face intense competition from other companies for collaborations with pharmaceutical and biotechnology companies, for establishing relationships with academic and research institutions, and for licenses to proprietary technology.

We are dependent on Bayer and third parties to manufacture and distribute Nexavar and Stivarga, and do not have the manufacturing expertise or capabilities to manufacture or distribute any current or future products.

Under our collaboration agreement and regorafenib agreement with Bayer, Bayer has the manufacturing responsibility to supply Nexavar and Stivarga for clinical trials and for commercialization. Should Bayer give up its right to co-develop Nexavar, we would have to manufacture Nexavar, or contract with another third party to do so for us. In addition, we have manufacturing responsibility for Kyprolis and oprozomib, which we currently manufacture through third-party contract manufacturers, and have not yet established back-up manufacturers for these compounds.

We lack the resources, experience and capabilities to manufacture Nexavar, Stivarga, Kyprolis, oprozomib or any other product candidate on our own and would require substantial funds and time to establish these capabilities. Consequently, we are, and expect to remain, dependent on third parties for manufacturing. These parties may encounter difficulties and delays in production scale-up, production yields, control and quality assurance, validation, regulatory status or shortage of qualified personnel. They may not perform as agreed or may not continue to manufacture our products for the time required to test or market our products. They may fail to deliver the required quantities of our products or product candidates on a timely basis and at commercially reasonable prices. Any production shortfall on the part of our third party manufacturers that impairs the supply, quality or price of starting materials, drug substance or drug product could have a material adverse effect on our business, financial condition and results of operations and future prospects.

We are dependent on single source suppliers and manufacturers for Kyprolis and have not developed backups. Disruptions to our Kyprolis supply chain could materially reduce our future earnings and prospects.

We currently rely on single source suppliers and manufacturers for commercial production of Kyprolis. Significant time and effort is required to develop backup vendors or to replace a vendor in the case of a stoppage. A loss or disruption with any one of our manufacturers or suppliers could disrupt supply of Kyprolis, possibly for a significant time period, and we may not have sufficient inventories to maintain supply before the manufacturer or supplier could be replaced or the disruption is resolved. For example, our contract manufacturer for Kyprolis drug product has experienced media fill failures on the line used to produce Kyprolis, and in January 2013 the line was shut down for scheduled upgrades. Future media fill failures, or delays in restarting the line following scheduled

upgrades, could delay the production of clinical or commercial supplies of Kyprolis, in which case we may not have sufficient inventory of Kyprolis product to satisfy our clinical and commercial requirements. In addition, marketed drugs and their contract manufacturing organizations are subject to continual review, including review and approval of their manufacturing facilities and the manufacturing processes, which can result in delays in the regulatory approval process and/or commercialization. Certain of the raw materials and components used in the manufacture of Kyprolis are provided by unaffiliated third-party suppliers and are specifically cited in the drug application, so that they must be obtained from that specific sole source and may not be obtained from another supplier unless and until the regulatory agency approved such supplier. Introducing a replacement or backup manufacturer or supplier for Kyprolis requires a lengthy regulatory and commercial process and there can be no guarantee that we could obtain necessary regulatory approvals in a timely fashion or at all. In addition, it is difficult to identify and select qualified suppliers and manufacturers with the necessary technical capabilities, and establishing new supply and manufacturing sources involves a lengthy and technical engineering process. Although we are in the process of developing secondary sources of manufacture and supply for Kyprolis, we have not yet done so and anticipate this process will require significant additional time to complete and we can provide no assurances that we will be successful. If our supply of Kyprolis is disrupted this would have a negative impact on sales that we anticipate would materially diminish our revenues and future prospects.

We rely on a network of specialty pharmacies and distributors.

A specialty pharmacy is a pharmacy that specializes in the dispensing of medications for complex or chronic conditions, which often require a high level of patient education and ongoing management. The use of specialty pharmacies and distributors involves certain risks, including, but not limited to, risks that these specialty pharmacies and distributors will:

- not provide us accurate or timely information regarding their inventories, the number of patients who are using our products or complaints about our products;
- reduce their efforts or discontinue to sell or support or otherwise not effectively sell or support our products;
- not devote the resources necessary to sell our products in the volumes and within the time frames that we expect;
- be unable to satisfy financial obligations to us or others; or
- cease operations.

We may never obtain regulatory approval for any other product candidates besides Nexavar, Kyprolis and Stivarga, or approval may be limited. In addition, we may not obtain additional regulatory approvals for Nexavar, Kyprolis and Stivarga.

We have limited experience managing regulatory filings and in negotiating product approval and licensure with regulatory authorities. We and Bayer may not succeed in obtaining additional regulatory approval of Nexavar, Kyprolis and Stivarga or our other product candidates on anticipated timelines or at all. Failure or delay in obtaining regulatory approvals would delay or prevent further commercialization of Kyprolis or commercialization of our other product candidates, in the United States and other countries. The review process for a regulatory marketing authorization, including a New Drug Application, or NDA, in the United States and a Marketing Authorization Application, or MAA, in Europe, is extensive, lengthy, expensive and uncertain. Regulatory agencies such as the FDA or the EMA have significant discretion during the review process and may determine to delay action on

or approval of a marketing approval application or limit or deny approval of a product candidate for many reasons. For example, the regulatory agencies may:

- conclude the marketing approval application fails to satisfy the requirements for approval;
- determine the data resulting from the clinical trials is not satisfactory, or investigators in those clinical trials could disagree with interpretation of the data;
- disagree with the number, design, size, conduct or implementation of clinical trials or conclude that the data fails to meet statistical or clinical significance or that there is an unmet medical need;
- find the data from preclinical studies and clinical studies insufficient to demonstrate that the study drug's clinical and other benefits outweighs its safety risks;
- disagree with the interpretation of data from preclinical studies or clinical trials;
- reject data generated at clinical trial sites and monitored by third party clinical research organizations, or CROs;
- determine that there was not proper oversight of third party CROs and clinical trials;
- reject stability data for commercial product;
- identify deficiencies in, or lack of control over, manufacturing processes, facilities or analytical methods or those of third party contract manufacturers;
- change or adversely impact their position due to unexpected or unpredictable external circumstances; and
- change their approval policies, adopt new regulations or provide new guidance with significant requirements not currently included or considered when seeking marketing approval.

Even if the FDA, EMA and other regulatory agencies approve marketing of our or Bayer's products, the regulatory agency may impose requirements, conditions and restrictions that could significantly increase costs or delay and limit our and Bayer's ability to successfully commercialize those products. The regulatory agency may require additional pre-clinical, clinical or retrospective observational studies or trials. The FDA may require a risk evaluation and mitigation strategy, or REMS, which could include a Medication Guide or a Conditions to Assure Safe Use requirement such as special patient monitoring/management to minimize risk of drug-related adverse events. These studies or trials may involve continued testing of the study drug and development of data, including clinical data, about the study drug's effects in various populations and any side effects associated with long-term use. The regulatory agency may require post-marketing studies or trials to investigate known serious risks or signals of serious risks or identify unexpected

serious risks and may require periodic status reports if new safety information develops. The regulatory agency may impose label restrictions to address safety concerns or limit the patient population. Such label restrictions could include limited indications and usage, expanded contraindications and expanded warnings and precautions. Any REMS plan, post-marketing studies, trials or commitments or label restrictions could significantly delay, limit, or prevent successful commercialization of a product or otherwise severely harm our business, financial condition and future prospects. Failure to conduct post-marketing studies in a timely manner may also result in substantial civil fines and even future withdrawal of approval to commercialize.

Our clinical trials for Nexavar or Kyprolis, and Bayer's clinical trials of Stivarga, could take longer to complete than we project or may not be completed at all.

The timing of initiation and completion of clinical trials may be subject to significant delays resulting from various causes, including actions by Bayer for Nexavar and/or Stivarga clinical trials,

conflicts regarding scheduling or competing clinical trials with participating clinicians and clinical institutions, difficulties in identifying and enrolling patients who meet trial eligibility criteria, modification of clinical trial designs, and shortages of available drug supply, including supply of comparator drugs or combination drugs for clinical and commercial purposes. We may face difficulties developing and sustaining relationships with Kyprolis development partners, including clinical research organizations, contract manufacturing organizations, key opinion leaders and clinical investigators. We may not complete clinical trials involving Nexavar, Kyprolis or any of our other product candidates as projected or at all.

We may not have the necessary capabilities to successfully manage the execution and completion of clinical trials in a way that leads to approval of Nexavar, Stivarga, Kyprolis or other product candidates for their target indications. In addition, we rely on Bayer, academic institutions, cooperative oncology organizations and clinical research organizations to conduct, supervise or monitor the majority of clinical trials involving Nexavar, Kyprolis and Stivarga. We have less control over the timing and other aspects of these clinical trials than if we conducted them entirely on our own. The timing of review by regulatory authorities is uncertain.

Development and commercialization of compounds that appear promising in research or development, including Phase 2 clinical trials, may be delayed or fail to reach later stages of development or the market for a variety of reasons including:

- nonclinical tests may show the product to be toxic or lack efficacy in animal models;
- clinical trial results may show the product to be less effective than desired or to have harmful or problematic side effects;
- regulatory approvals may not be received, or may be delayed due to factors such as slow enrollment in clinical studies, extended length of time to achieve study endpoints, additional time requirements for data analysis or preparation of an Investigational New Drug, or IND, application, discussions with regulatory authorities, requests from regulatory authorities for additional preclinical or clinical data, analyses or changes to study design, including possible changes in acceptable trial endpoints, or unexpected safety, efficacy or manufacturing or quality issues, changes in policy or objectives at regulatory authorities, and regulatory filings submitted on competing drugs that could alter the regulatory prospects of our drugs;
- difficulties formulating the product, scaling the manufacturing process or in validating or getting approval for manufacturing;
- manufacturing costs, pricing or reimbursement issues, or other factors may make the product uneconomical;
- proprietary or contractual rights of others and their competing products and technologies may prevent our product from being developed or commercialized or may increase the cost of doing so; and
- contractual rights of our collaborators or others may prevent our product from being developed or commercialized or may increase the cost of doing so.

Failure to continue to successfully develop Stivarga or Kyprolis could harm their commercialization, and failure to successfully launch or commercialize Kyprolis or Stivarga for these or any other reasons would significantly harm our business and future prospects.

Even though Kyprolis is approved by the FDA and even if Kyprolis is approved by other regulatory authorities, we may not obtain adequate coverage or reimbursement from third-party payers, which would harm our business

In order to successfully commercialize Kyprolis, we must obtain coverage and reimbursement by private and public insurers. In addition we must establish a mechanism to effectively distribute Kyprolis to physician offices. We have no prior experience in building or maintaining an access, reimbursement and distribution infrastructure, which is difficult and time consuming, and requires substantial financial and other resources. Factors that may hinder our efforts include inability to recruit, retain and manage adequate numbers of effective personnel, and an inability to establish or maintain relationships with government agencies, insurers and distributors.

Our sales of Kyprolis are dependent on the availability and extent of coverage and reimbursement from third-party payers, including government healthcare programs and private insurance plans. We rely on the reimbursement coverage by federal and state government programs such as Medicare and Medicaid in the United States and will rely on equivalent programs in other countries, once we receive regulatory approval for those countries. We also rely on coverage and reimbursement from private pharmaceutical insurers in the United States. In the event we seek approvals to market Kyprolis in foreign territories, we will need to work with the government-sponsored healthcare systems in Europe and other foreign jurisdictions that are the primary payers of healthcare costs in those regions. Governments and private payers may regulate prices, reimbursement levels and/or access to Kyprolis in order to control costs or to affect levels of use of our products. We cannot predict the availability or level of coverage and reimbursement for Kyprolis or our product candidates and a reduction in coverage and/or reimbursement for our products could have a material adverse effect on our product sales and results of operations. In addition, our estimates of discounts and reserves against our gross sales of Kyprolis, also referred to as gross to net adjustments will continue to be informed and evolve as we build a history of coverage and reimbursement for Kyprolis, which for some categories like Medicaid rebates and returns, may take up to a full year after launch.

We expect that many of the patients in the United States who seek treatment with Kyprolis will be eligible for Medicare benefits. Other patients may be covered by private health plans. The Medicare program is administered by the Centers for Medicare & Medicaid Services, or CMS, and coverage and reimbursement for products and services under Medicare are determined pursuant to statute, regulations promulgated by CMS, and CMS's subregulatory coverage and reimbursement determinations. It is difficult to predict exactly how CMS may apply those regulations and policy determinations to Kyprolis, and those regulations and interpretive determinations are subject to change. Moreover, the procedures and criteria by which CMS makes coverage and reimbursement determinations and the reimbursement amounts established by statute are subject to change, particularly because of budgetary pressures facing the Medicare program.

Medicare Part B provides limited coverage of outpatient drugs that are furnished "incident to" a physician's services. Generally, "incident to" drugs are covered only if they satisfy certain criteria, including that they are of the type that is not usually self-administered by the patient and they are reasonable and necessary for a medically accepted diagnosis or treatment. To date Kyprolis is generally covered under Medicare Part B and the Medical benefit for private insurers. Medicare Part B generally pays for drugs provided in a hospital outpatient setting and in physicians' offices under a payment methodology using average sales price, or ASP, information. The U.S. Department of Health and Human Services Inspector General may compare the ASP for a drug or biological to the widely available market price and the Medicaid Average Manufacturer Price for that drug or biological, which could lead to future reductions in Medicare payment rates. Congress has considered reducing Medicare Part B payment rates, and legislation such as that related to "sequestration," which refers to an automatic spending cut in the federal budget effected by funds being "sequestered" by the U.S. Treasury, could be enacted in the future reducing reimbursement levels. We have no experience

marketing a Medicare Part B drug, or reporting ASP information, as is required by CMS. If we fail to collect and report information correctly and on a timely basis, our business could be harmed. If we are found to have made a misrepresentation in the reporting of ASP, we may be subject to significant civil and criminal penalties, including exclusion from federal health care programs.

By statute, new drugs administered in hospital outpatient departments that are granted "pass-through status" also are reimbursed at ASP plus six percent for two to three years after they are granted pass-through status. Kyprolis has not yet been granted pass-through status and claims will initially be reimbursed by Medicare Part B at 95% of the Average Wholesale Price, or AWP, until Kyprolis is assigned a product specific product code. CMS establishes the hospital outpatient payment rates by regulation for drugs that do not have pass-through status. For 2012, these drugs were reimbursed at ASP plus four percent if they have an average cost per day exceeding $75; drugs with an average cost per day less than $75 are not separately reimbursed, and CMS packages payment into the payment for the associated procedure (an ambulatory payment classification group) as part of the overall cost of the outpatient service provided to Medicare beneficiaries. In future years, CMS could change both the payment rate and the average cost threshold, and these changes could adversely affect payment for Kyprolis.

We expect that Kyprolis will be made available to patients that are eligible for Medicaid benefits. A condition of federal funds being made available to cover our products under Medicaid and Medicare Part B is our participation in the Medicaid drug rebate program. Under the Medicaid rebate program, we must pay a rebate to each state Medicaid program for each unit of our drug paid for by those programs. The rebate amount for a drug varies by quarter, and is based on pricing data reported by us on a monthly and quarterly basis to CMS.

The Patient Protection and Affordable Care Act and the Health Care and Education Affordability Reconciliation Act, or collectively PPACA, is expected to impact the United States pharmaceutical industry substantially, including with regard to how health care is financed by both governmental and private insurers. Among the provisions of PPACA of greatest importance to the pharmaceutical industry are the following:

- an annual, nondeductible fee on any entity that manufactures or imports certain branded prescription drugs and biologic agents, apportioned among these entities according to their market share in certain government healthcare programs, not including orphan drug sales;

- an increase in the rebates a manufacturer must pay under the Medicaid Drug Rebate Program to 23.1% and 13% of the average manufacturer price for branded and generic drugs, respectively;

- a new Medicare Part D coverage gap discount program, in which manufacturers must agree to offer 50% point-of-sale discounts to negotiated prices of applicable brand drugs to eligible beneficiaries during their coverage gap period, as a condition for the manufacturer's outpatient drugs to be covered under Medicare Part D;

- extension of manufacturers' Medicaid rebate liability to covered drugs dispensed to individuals who are enrolled in Medicaid managed care organizations;

- expansion of eligibility criteria for Medicaid programs by, among other things, allowing states to offer Medicaid coverage to additional individuals and by adding new mandatory eligibility categories for certain individuals with income at or below 133% of the Federal Poverty Level beginning in 2014, thereby potentially increasing manufacturers' Medicaid rebate liability;

- expansion of the entities eligible for discounts under the Public Health Service pharmaceutical pricing program;

new requirements to report certain financial arrangements with physicians and teaching hospitals, as defined in PPACA and its implementing regulations, including reporting any payment or "transfer of value" made or distributed to teaching hospitals, prescribers and other healthcare providers, and reporting any ownership and investment interests held by physicians and their immediate family members and applicable group purchasing organizations during the preceding calendar year, with data collection to be required no earlier than January 1, 2013 and reporting to be required at a later date yet to be specified;

expansion of health care fraud and abuse laws, including the False Claims Act and the Anti-Kickback Statute, new government investigative powers, and enhanced penalties for noncompliance;

a licensure framework for follow-on biologic products; and

a new Patient-Centered Outcomes Research Institute to oversee, identify priorities in, and conduct comparative clinical effectiveness research, along with funding for such research.

On June 28, 2012, the United States Supreme Court upheld the constitutionality of PPACA, excepting certain provisions, noted above, that would have required states to expand their Medicaid programs or risk losing all of the state's Medicaid funding. At this time, it remains unclear whether there will be any further changes made to PPACA, whether in part or in its entirety. Moreover, state and federal legislative and regulatory proposals aimed at reforming the healthcare system in the United States continue to be proposed, the effect of which, if enacted, could adversely impact our product sales and results of operations.

U.S. and foreign policymakers and payers continue to express significant interest in promoting reforms aimed at containing healthcare costs, improving quality and/or expanding access. In many international markets, governments control the prices of prescription pharmaceuticals, including through the implementation of reference pricing, price cuts, rebates, revenue-related taxes and profit control. The use of formal economic metrics has been increasing across Europe, as well as in several emerging markets throughout the world, to determine whether or not a new product will be reimbursed and, increasingly, in setting the maximum price at which the product will be reimbursed. With increased budgetary constraints, payers in many countries employ a variety of measures to exert downward price pressure such as international price referencing, therapeutic reference pricing (e.g., setting the reimbursement rate for a given class of agents at the lowest price within the class), increasing mandates or incentives for generic substitution, and government-mandated discounts and price cuts.

In the United States, reimbursement rates may vary according to the use of the drug and the clinical setting in which it is used, may be based on payments allowed for lower-cost products that already are reimbursed, may be incorporated into existing payments for other products or services, and may reflect budgetary constraints and/or imperfections in Medicare or Medicaid data used to calculate these rates. Net prices for products are reduced by mandatory discounts or rebates required by government health care programs and privately-negotiated discounts. While we will implement policies in an effort to comply with mandated reimbursement rates, the United States government, state governments and private payers frequently pursue actions against pharmaceutical and biotechnology companies alleging that the companies have overstated prices in order to inflate reimbursement rates. Any such action could adversely affect the pricing of and the commercial success of our products and expose us to civil money penalties or other liability.

The availability of federal funds under Medicaid and Medicare Part B to pay for Kyprolis and any other products that are approved for marketing also is conditioned on our participation in the Public Health Service 340B drug pricing program. The 340B drug pricing program requires participating manufacturers to agree to charge statutorily-defined covered entities no more than the 340B "ceiling price" for the manufacturer's covered outpatient drugs. These covered entities include hospitals that

serve a disproportionate share of poor Medicare beneficiaries, as well as a variety of community health clinics and other recipients of health services grant funding. PPACA expanded the 340B program to include additional entity types: certain free standing cancer hospitals, critical access hospitals, rural referral centers and sole community hospitals, each as defined by the Act. The 340B ceiling price for a drug is calculated using a statutory formula that is based on the AMP and Medicaid rebate amount for the drug. To the extent PPACA, as discussed above, changes the statutory and regulatory definitions of AMP and the Medicaid rebate amount, these changes will also affect our 340B ceiling price for Kyprolis or any other of our products that are approved for marketing. Any revisions to previously reported Medicaid pricing data also may require revisions to the 340B ceiling prices that were based on those data and could require the issuance of refunds.

If Nexavar does not continue to be broadly adopted for the treatment of unresectable liver cancer, our business would be harmed. If our ongoing and planned clinical trials fail to demonstrate that Nexavar is safe and effective for additional indications or we are unable to obtain necessary approvals for other uses, we will be unable to expand the commercial market for Nexavar and our business may be harmed or fail.

The market size for Nexavar in treating unresectable liver cancer depends on several factors, including educating treating physicians on the appropriate use of Nexavar and the management of patients who are receiving Nexavar. Achieving these goals may be difficult as liver cancer patients typically have underlying liver disease and other comorbidities and can be treated by a variety of medical specialists. In addition, screening, diagnostic and treatment practices can vary significantly by region. Further, liver cancer is common in many regions in the developing world where the healthcare systems are limited and reimbursement for Nexavar is limited or unavailable, which will likely limit or slow adoption. While we have established Nexavar as part of the treatment paradigm for liver cancer, we may not be able to successfully achieve its full market potential for this indication. In addition, certain countries require pricing to be established before reimbursement for this indication may be obtained and in some Asian Pacific countries where most of the current market is private pay, these approvals require prolonged negotiations with the governments, potentially including multiple government agencies. In addition, we may not receive or maintain pricing approvals at favorable levels or at all, which could harm our ability to broadly market Nexavar.

Nexavar has not been approved in any indications other than unresectable liver cancer and advanced kidney cancer. We and Bayer are currently conducting a number of clinical trials of Nexavar; however, our clinical trials may fail to demonstrate that Nexavar is safe and effective in other indications, and Nexavar may not gain additional regulatory approval, which would limit the potential market for the product and harm our future prospects. If we are not able to obtain approval for label expansion or alternative delivery mechanisms, we will have incurred significant clinical trial costs without corresponding benefits, our future prospects may suffer and our business and financial condition could be materially and adversely affected. Success in one or even several cancer types does not indicate that Nexavar would be approved or have successful clinical trials in other cancer types. Regulatory requirements change over time, including acceptable clinical endpoints. We may be unable to satisfy new requirements or expectations of regulatory authorities and hence, Nexavar may never be approved in additional indications.

Even if our products receive regulatory approval, guidelines and recommendations published by various organizations may affect the uptake, adoption and/or use of those products.

Government agencies issue regulations and guidelines directly applicable to us and to our products and to Bayer's products. In addition, professional societies, practice management groups, private health/science foundations and organizations involved in various diseases from time to time publish guidelines or recommendations to the medical and patient communities. These various sorts of recommendations may relate to such matters as product usage, dosage, route of administration and use of related or

competing therapies. Such recommendations or changes to such recommendations or other changes or other guidelines advocating alternative therapies could result in decreased use of Nexavar, Kyprolis and Stivarga, which may adversely affect our results of operations.

We are dependent upon our collaborative relationship with Bayer to further develop, manufacture and commercialize Nexavar and Stivarga.

Our success for developing, manufacturing and commercializing Nexavar and Stivarga depends in large part upon our relationship with Bayer. If we are unable to maintain our collaborative relationship with Bayer, we may be unable to continue development, manufacturing and marketing activities at our own expense. If we were able to do so on our own, this would significantly increase our capital and infrastructure requirements, would necessarily impose delays on development programs, may limit the indications we are able to pursue and could prevent us from effectively developing and commercializing Nexavar and Stivarga. Disputes with Bayer may delay or prevent us from further developing, manufacturing or commercializing or increasing the sales of Nexavar, and could lead to additional disputes with Bayer, which could be time consuming and expensive. As permitted under our amended collaboration agreement and regorafenib agreement with Bayer, we may develop Nexavar and/or Stivarga in certain indications at our own expense. If we were to do so, this would increase our research and development costs, could impose delays on other development programs, and/or could limit the indications we are able to pursue.

We are subject to a number of risks associated with our dependence on our collaborative relationship with Bayer, including:

- unfavorable decisions by Bayer regarding the amount and timing of resource expenditures for the development and commercialization of Nexavar and Stivarga;
- possible disagreements as to development plans, clinical trials, regulatory marketing or sales;
- our inability to co-promote Nexavar or Stivarga in any country outside the United States, which makes us solely dependent on Bayer to promote Nexavar and Stivarga in foreign countries;
- Bayer's right to terminate the collaboration agreement on limited notice in certain circumstances involving our insolvency or material breach of the agreement;
- loss of significant rights if we fail to meet our obligations under the collaboration agreement;
- adverse regulatory or legal action against Bayer resulting from failure to meet healthcare industry compliance requirements in the promotion and sale of Nexavar and/or Stivarga, including federal and state reporting requirements;
- changes in key management personnel at Bayer, including Bayer's representatives on the collaboration's executive team; and
- disagreements with Bayer regarding interpretation or enforcement of the collaboration agreement and/or the regorafenib agreement.

We have limited ability to direct Bayer in its promotion of Nexavar and Stivarga and we may be unable to obtain any remedy against Bayer. Bayer may not have sufficient expertise to promote or obtain reimbursement for oncology products in foreign countries

and may fail to devote appropriate resources to this task. In addition, Bayer may establish a sales and marketing infrastructure for Nexavar outside the United States that is too large and expensive in view of the magnitude of the Nexavar sales opportunity. We are at risk with respect to the success or failure of Bayer's commercial decisions related to Nexavar and Stivarga as well as the extent to which Bayer succeeds in the execution of its strategy.

Bayer's development of other products, including Stivarga, may provide Bayer incentives to develop and commercialize Nexavar that are different from our own. In preparation for approval and commercialization of Stivarga in the treatment of metastatic colon cancer and GIST we have elected to increase the number of sales representatives necessary to promote Nexavar and Stivarga. This may result in disrupting many current relationships with physicians. The new representatives and current representatives may not be able to have access to or will have a delay in access to the physicians. This could result in lower sales of Nexavar and Stivarga for the time period until access is established or lower sales permanently if access is not fully re-established. In addition, selling two products is more complex than selling a single product, and some representatives may be slow to or unable to make this transition, resulting in lower sales in their territory.

Under the terms of the collaboration agreement, we and Bayer must agree on the development plan for Nexavar. If we and Bayer cannot agree, clinical trial progress could be significantly delayed or halted. Bayer has the right, upon 60 days' notice, to cease co-funding of the development of Nexavar. If Bayer ceases co-funding Nexavar development, further development of Nexavar could be delayed and we may be unable to fund the development costs on our own and may be unable to find a new collaborator. If we or Bayer cease funding development of Nexavar under the collaboration agreement, then the party which ceases funding will be entitled to receive a royalty, but not to share in profits.

In addition, Bayer has the right, which it is not currently exercising, to nominate a member to our board of directors as long as we continue to collaborate on the development of a compound. Because of these rights, ownership and voting arrangements, our stockholders may not be able to effectively control the election of all members of the board of directors and our ability to independently determine all corporate actions could be diminished.

Moreover, we are highly dependent on Bayer for timely and accurate information regarding any revenues realized from sales of Nexavar and Stivarga and the costs incurred in developing and selling Nexavar, in order to accurately report our results of operations. If we do not receive timely and accurate information or incorrectly estimate activity levels associated with the co-promotion and development of Nexavar and Stivarga, we could be required to record adjustments in future periods and may be required to restate our results for prior periods. Such inaccuracies or restatements could cause a loss of investor confidence in our financial reporting or lead to claims against us, harming our operations and future prospects.

Our collaboration agreement with Bayer will terminate when patents expire that were issued in connection with product candidates discovered under that agreement, or at the time when neither we nor Bayer are entitled to profit sharing under that agreement, whichever is later. Our right to royalties on the sale of Stivarga will terminate with expiration of Stivarga patents. The worldwide patents and patent applications covering Nexavar and Stivarga are owned by Bayer and certain patents are licensed to us through our collaboration agreement and regorafenib agreement. We have limited control over the filing, strategy, or prosecution of the Nexavar and Stivarga patent applications and no control of enforcement or defense of the patents outside the United States.

We may need additional funds, our future access to capital is uncertain, and unstable market and economic conditions may have serious adverse consequences on our business.

We may need additional funds to conduct the costly and time-consuming activities related to the development and commercialization of Nexavar and Kyprolis and our other product candidates, including manufacturing, clinical trials and regulatory approval. Also, we may need funds to develop our early stage product candidates, to acquire rights to additional product candidates, or acquire new or complementary businesses. Our future capital requirements will depend upon a number of factors, including:

- revenue from our product sales;

global product development and commercialization activities;

the cost involved in enforcing patents against third parties and defending claims by third parties;

the costs associated with acquisitions or licenses of additional products;

the cost of acquiring new or complementary businesses;

competing technological and market developments; and

future fee and milestone payments

We may not be able to raise additional capital on favorable terms, or at all. If we are unable to obtain additional funds, we may not be able to fund our share of commercialization expenses and clinical trials. We may also have to curtail operations or obtain funds through collaborative and licensing arrangements that may require us to relinquish commercial rights or potential markets or grant licenses on terms that are unfavorable to us.

If we change our development plans, acquire rights to or license additional products, or seek to acquire new or complementary businesses, we may need additional funds sooner than we expect. In addition, we anticipate that our expenses related to Kyprolis will increase over the next several years. While these costs are unknown at the current time, we may need to raise additional capital and may be unable to do so.

Our general business may be adversely affected by global economic difficulties, a volatile business environment and continued unpredictable and unstable market conditions. If the equity and credit markets do not sustain improvement or begin to deteriorate again, it may make any necessary future debt or equity financing more difficult, more costly and more dilutive, and may result in adverse changes to product reimbursement and pricing and sales levels, which would harm our operating results. Failure to secure any necessary financing in a timely manner and on favorable terms could have a material adverse effect on our growth strategy, financial performance and future prospects and could require us to delay or abandon clinical development plans or plans to acquire additional technology. There is also a possibility that our stock price may decline, due in part to the volatility of the stock market and the general economic downturn, such that we would lose our status as a Well-Known Seasoned Issuer, which allows us to more rapidly and more cost-effectively seek to raise funds in the public markets.

Additionally, other challenges resulting from the current economic environment include fluctuations in foreign currency exchange rates, global pricing pressures, increases in national unemployment impacting patients' ability to access drugs, increases in uninsured or underinsured patients affecting their ability to afford pharmaceutical products and increased U.S. free goods to patients. There is a risk that one or more of our current service providers, manufacturers and other partners may not survive these difficult economic times, which would directly affect our ability to attain our operating goals on schedule and on budget. Further dislocations in the credit market may adversely impact the value and/or liquidity of marketable securities owned by us.

Our operating results could be adversely affected by product sales occurring outside the United States and fluctuations in the value of the United States dollar against foreign currencies or unintended consequences from our currency contracts.

A majority of Nexavar sales are generated outside of the United States, and a significant percentage of Nexavar commercial and development expenses are incurred outside of the United States. Under our collaboration agreement, when these sales and expenses are translated into U.S. dollars by Bayer in determining amounts payable to us or payable by us, we are exposed to fluctuations in foreign currency exchange rates. We also incur a significant percentage of research and development expenses for Kyprolis and our earlier-stage development products in currencies other than the U.S.

dollar. We enter into transactions to manage our exposure to fluctuations in foreign currency exchange rates. Such transactions may expose us to the risk of financial loss in certain circumstances, including instances in which there is a change in the expected differential between the underlying exchange rate in the contracts and actual exchange rate.

The primary foreign currencies in which we have exchange rate fluctuation exposure are the Euro and the British Pound. As we expand our business geographically, we could be exposed to exchange rate fluctuation in other currencies. Exchange rates between these currencies and the U.S. dollar have fluctuated significantly in recent years and may do so in the future. Hedging foreign currencies can be difficult, especially if the currency is not freely traded. We cannot predict the impact of future exchange rate fluctuations on our operating results.

If serious adverse side effects are associated with Nexavar, Stivarga or Kyprolis, our business could be harmed.

The FDA-approved package inserts for Nexavar, Kyprolis and Stivarga includes several warnings relating to observed adverse reactions. For example, severe and sometimes fatal hepatotoxicity has been observed in clinical studies of Stivarga. These adverse reactions are highlighted as a boxed warning in the labeling for Stivarga, which could increase regulatory scrutiny for adequately addressing risk information in promotional messaging. With commercial use and additional clinical trials of these products, we and Bayer have updated and expect to continue to update adverse reactions listed in the package insert to reflect current information. If additional adverse reactions emerge, or a pattern of severe or persistent previously observed side effects is observed in the relevant patient populations, the FDA or other regulatory agencies could modify or revoke marketing approval of any product or we may choose to withdraw one or more products from the market. If this were to occur, we may be unable to obtain marketing approval in additional indications. In addition, if patients receiving Nexavar, Kyprolis or Stivarga were to suffer harm as a result of their use of these products, these patients or their representatives may bring claims against us. These claims, or the mere threat of these claims, could have a material adverse effect on our business and results of operations.

We expect to seek additional regulatory approvals of Kyprolis in the United States and other countries. We have observed and reported safety and adverse events in Kyprolis clinical trials, which may increase the risk that FDA, or other regulatory agencies, could reject future application(s) for marketing approval. Similarly Bayer is seeking additional regulatory approval for Stivarga, and has reported safety and adverse events in Stivarga trials, which may increase the risk that regulatory agencies could reject additional marketing approval for Stivarga. Even if Bayer succeeds in obtaining multiple regulatory approvals for Stivarga, we expect that their package inserts, if approved, will include information related to safety and adverse events, which could limit the market potential or reimbursability of either or both products

If previously unforeseen and unacceptable side effects are observed in Nexavar, Kyprolis, or Stivarga, we may be unable to proceed with further clinical trials, to seek or obtain regulatory approval in one or more indications, or to realize full commercial benefits of our products. In clinical trials, patients may be treated with Nexavar, Kyprolis, or Stivarga as a single agent or in combination with other therapies. During the course of treatment, these patients may die or suffer adverse medical effects for reasons unrelated to our products, including adverse effects related to the products that are administered in combination with our products. These adverse effects may impact the interpretation of clinical trial results, which could lead to adverse conclusions regarding the toxicity or efficacy of Nexavar, Kyprolis, or Stivarga.

We are subject to extensive government regulation, which can be costly, time consuming and subject us to unanticipated delays. We may incur significant liability if it is determined that we are in violation of federal and state regulations related to the promotion of drugs in the United States or elsewhere.

If we have disagreements with Bayer regarding ownership of clinical trial results or regulatory approvals for Nexavar, and the FDA refuses to recognize Onyx as holding, or having access to, the regulatory approvals necessary to commercialize Nexavar, we may experience delays in or be precluded from marketing Nexavar.

For Kyprolis, we are responsible for managing communications with regulatory agencies, including filing investigational new drug applications, filing new drug applications, submission of promotional materials and generally directing the regulatory processes. We have limited experience directing such activities and may not be successful with our planned development strategies, on the planned timelines, or at all. If we fail to conduct any required post-approval studies or if the studies fail to verify that any of our product candidates are safe and effective, our FDA approval could be revoked.

If we or Bayer fail to comply with applicable regulatory requirements we could be subject to penalties, including fines, suspensions of regulatory approval, product recall, seizure of products and criminal prosecution.

To date, the FDA has approved Nexavar only for the treatment of advanced kidney cancer and unresectable liver cancer. Physicians are not prohibited from prescribing Nexavar for the treatment of diseases other than advanced kidney cancer or unresectable liver cancer, however, we and Bayer are prohibited from promoting Nexavar for any non-approved indication, often called "off label" promotion. Likewise, to date, the FDA has approved Kyprolis only for the treatment of patients with multiple myeloma who have received at least two prior therapies, including bortezomib and an immunomodulatory agent, and have demonstrated disease progression on or within 60 days of completion of the last therapy; and Stivarga only for the treatment of patients with metastatic colorectal cancer, or mCRC, who have been previously treated with currently available therapies. Although physicians are not prohibited from prescribing Kyprolis or Stivarga for the treatment of diseases other than the FDA-approved indication, we are prohibited from promoting Kyprolis or Stivarga for any other indications. The FDA and other regulatory agencies actively enforce regulations prohibiting off label promotion and the promotion of products for which marketing authorization has not been obtained. A company that is found to have improperly promoted an off label use may be subject to significant liability, including civil and administrative remedies, as well as criminal sanctions.

We engage in the support of medical education activities and engage investigators and potential investigators interested in our clinical trials. Although we believe that all of our communications regarding Nexavar and Kyprolis are in compliance with the relevant regulatory requirements, the FDA or another regulatory authority may disagree, and we may be subject to significant liability, including civil and administrative remedies as well as criminal sanctions.

Certain federal and state healthcare laws and regulations pertaining to fraud and abuse are and will be applicable to our business. For example, in the United States, there are federal and state anti-kickback laws that prohibit the payment or receipt of kickbacks, bribes or other remuneration intended to induce the purchase or recommendation of healthcare products and services or reward past purchases or recommendations. Violations of these laws can lead to civil and criminal penalties, including fines, imprisonment and exclusion from participation in federal healthcare programs. A number of states have enacted laws that require pharmaceutical companies to track and report payments, gifts and other benefits provided to physicians and other health care professionals and entities. Similarly, Section 6002 of PPACA requires pharmaceutical companies to report to the federal government certain payments and transfers of value to physicians and teaching hospitals and certain ownership and investment interests held by physicians or their immediate family members in applicable manufacturers. Other state laws require pharmaceutical companies to adopt and or disclose specific

compliance policies to regulate the company's interactions with healthcare professionals. Some states, such as Massachusetts, Minnesota, and Vermont, impose an outright ban on certain gifts to physicians. Violations of some of these laws may result in substantial fines. These laws affect our promotional activities by limiting the kinds of interactions we may have with hospitals, physicians or other potential purchasers or users of our products. Both the disclosure laws and gift bans impose additional administrative and compliance burdens on us. These laws are broadly written, and it is often difficult to determine precisely how a law will be applied in specific circumstances. If an employee were to offer an inappropriate gift to a customer, we could be subject to a claim under an applicable federal and state law. Similarly if we fail to comply with a reporting requirement, we could be subject to penalties under applicable federal or state laws.

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 Health Insurance Portability and Accountability Act of 1996, or 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 Data Privacy Act, 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.

As we expand our development and commercialization activities outside of the United States, we will be subject to an increased risk of inadvertently conducting activities in a manner that violates the U.S. Foreign Corrupt Practices Act and similar laws. If that occurs, we may be subject to civil or criminal penalties which could have a material adverse effect on our business, financial condition, results of operations and growth prospects.

We are subject to the U.S. Foreign Corrupt Practices Act, or FCPA, which prohibits corporations and individuals from paying, offering to pay, or authorizing the payment of anything of value to any foreign government official, government staff member, political party, or political candidate in an attempt to obtain or retain business or to otherwise influence a person working in an official capacity. We are also subject to the UK Anti-Bribery Act, which prohibits both domestic and international bribery, as well as bribery across both public and private sectors.

In the course of establishing and expanding our commercial operations and seeking regulatory approvals outside of the United States, we will need to establish and expand business relationships with various third parties, such as independent contractors, vendors, advocacy groups and physicians, and we will interact more frequently with foreign officials, including regulatory authorities and physicians employed by state-run healthcare institutions who may be deemed to be foreign officials under the FCPA, UK Anti-Bribery Act or similar laws of other countries that may govern our activities. Any interactions with any such parties or individuals where compensation is provided that are found to be in violation of such laws could result in substantial fines and penalties and could materially harm our business. Furthermore, any finding of a violation under one country's laws may increase the likelihood that we will be prosecuted and be found to have violated another country's laws. If our business practices outside the United States are found to be in violation of the FCPA, UK Anti-Bribery Act or

other similar law, we may be subject to significant civil and criminal penalties which could have a material adverse effect on our business, financial condition, results of operations, liquidity and growth prospects.

The market may not accept our products and we may be subject to pharmaceutical pricing and third-party reimbursement pressures.

Nexavar, Kyprolis, Stivarga, or our other product candidates that may be approved may not gain market acceptance among physicians, patients, healthcare payers and/or the medical community or the market may not be as large as forecasted. Third-party payers and governments are increasingly challenging the pricing of medical products and services, especially in global markets, and their reimbursement practices may affect the price levels for Nexavar, Kyprolis or Stivarga, if approved, or any other future product. Governments outside of the United States may increase their use of risk-sharing programs, which will only pay for a drug after it demonstrates efficacy in a given patient. In addition, governments may increasingly rely on Health Technology Assessments to determine payment policy for cancer drugs. Health Technology Assessments are used by governments to assess if health services are safe and cost-effective. In addition, the market for our products may be limited by third-party payers who establish lists of approved products and do not provide reimbursement for products not listed. If our products are not on the approved lists in one or more countries, our sales may suffer. Non-government organizations can influence the use of our products and reimbursement decisions for our products in the United States and elsewhere. For example, the National Comprehensive Cancer Network, or NCCN, a not-for-profit alliance of cancer centers, has issued guidelines for the use of Nexavar in the treatment of advanced kidney cancer and unresectable liver cancer. These guidelines may affect treating physicians' use of Nexavar.

Nexavar's success in Europe and other regions, particularly in Asia Pacific, could also depend on obtaining and maintaining government reimbursement. For example, in Europe and in many other international markets, patient access is limited for medicines that are not reimbursed by the government. Negotiating prices with governmental authorities can delay commercialization by up to twelve months or more. Even if reimbursement is available, reimbursement policies may adversely affect sales and profitability of Nexavar. In addition, in Europe and in many international markets, governments control the prices of prescription pharmaceuticals and expect prices of prescription pharmaceuticals to decline over the life of the product or as volumes increase. In the Asia-Pacific region, excluding Japan, China leads in Nexavar sales, however, reimbursement typically requires multiple steps. Also, in December 2009, health authorities in China published a new National Reimbursement Drug List, or NRDL, which lists medicines that are expected to be sold at government-controlled prices. There were no targeted oncology drugs, including Nexavar, on the NRDL, however, the Ministry of Human Resource and Social Security, the group responsible for developing the NDRL, could establish a mechanism and framework for reimbursement of high-value innovative products, such as targeted oncology drugs. Reimbursement policies are subject to change due to economic, political or competitive factors. We believe that this will continue into the foreseeable future as governments struggle with escalating health care spending.

In the European Union, governments influence the price of pharmaceutical products through their pricing and reimbursement rules and control of national healthcare systems that fund a large part of the cost of such products to consumers. The approach taken varies from member state to member state. Some jurisdictions operate positive and/or negative list systems under which products may be marketed only once a reimbursement price has been agreed. Other member states allow companies to fix their own prices for medicines, but monitor and control company profits. The downward pressure on healthcare costs in general, particularly prescription drugs, has become very intense. As a result, increasingly high barriers are being erected to the entry of new products, as exemplified by the role of the National Institute for Health and Clinical Excellence in the United Kingdom, which evaluates the

data supporting new medicines and passes reimbursement recommendations to the government. In addition, in some countries cross-border imports from low-priced markets (parallel imports) exert commercial pressure on pricing within a country.

Forecasting sales of Kyprolis may be difficult and revenue recognition may be deferred. If our revenue projections are inaccurate or revenue is deferred and our business forecasting and planning decisions are not reflected in our actual results, our business may be harmed and our future prospects may be adversely affected.

Kyprolis may not be adopted rapidly, or at all, by physicians. Factors that can affect the rate of adoption and that can increase the difficulty of forecasting sales include the following:

physician and patient unfamiliarity with Kyprolis;

cautionary prescribing behavior due to concerns regarding the safety and risk-benefit of Kyprolis

cautionary prescribing behavior due to lack of reimbursement history for Kyprolis;

confusion and questions relating to the label;

difficulty in identifying appropriate patients for treatment with Kyprolis;

the cost of the product, which is purchased by the prescriber on a buy and bill basis;

other aspects of physician education;

treatment guidelines issued by government and non-government agencies;

types of cancer for which the product is approved;

timing of market entry relative to competitive products;

availability of alternative therapies;

price of our product relative to alternative therapies, including generic versions of our products, or generic versions of innovative products that compete with our products;

patients' reliance on patient assistance programs, under which we provide free drug;

rates of returns and rebates;

uncertainty of launch trajectory;

our ability to manufacture and deliver Kyprolis in commercially sufficient quantities;

extent of marketing efforts by us and third-party distributors or agents retained by us; and

side effects or unfavorable publicity concerning our products or similar products.

The extent to which any of these or other factors individually or in the aggregate may impact future sales of Kyprolis is uncertain and difficult to predict. Our management must make forecasting decisions regarding future revenue in the course of business planning despite this uncertainty, and actual results of operations may deviate materially from projected results. This may lead to inefficiencies and increased difficulties in operational planning. If our revenues from Kyprolis sales are lower than we anticipate or revenue is deferred, we will incur costs in the short term that will result in losses that are unavoidable. A shortfall in our revenue would have a direct impact on our cash flow and on our business generally. In addition, fluctuations in our quarterly results can adversely and significantly affect the market price of our common stock.

Our financial results depend on management's selection of accounting methods and certain assumptions and estimates

Our accounting policies and methods are fundamental to how we record and report our financial condition and results of operations. Our management must exercise judgment in selecting and applying many of these accounting policies and methods so they comply with generally accepted accounting principles and reflect management's judgment of the most appropriate manner to report our financial condition and results. In some cases, management must select the accounting policy or method to apply from two or more alternatives, any of which may be reasonable under the circumstances, yet may result in our reporting materially different results than would have been reported under a different alternative.

Certain accounting policies are critical to presenting our financial condition and results. The preparation of our financial statements require us to make significant estimates, assumptions and judgments that affect the amounts of assets, liabilities, revenues and expenses and related disclosures. Significant estimates made by us include assumptions used in the determination of revenue recognition and the calculation of reserves, the fair value of marketable securities, revenue from the Bayer collaboration agreement, multiple element arrangements, the effect of business combinations, fair value measurement of tangible and intangible assets and liabilities, goodwill and other intangible assets, fair value of convertible senior notes, research and development expenses, stock-based compensation and the provision for income taxes. For example, our management exercised judgment in determining the appropriate revenue recognition policy for product sales of Kyprolis. Although we base our estimates and judgments on historical experience, our interpretation of existing accounting literature and on various other assumptions that we believe to be reasonable under the circumstances, if our interpretation or application of existing accounting literature is deemed to be materially incorrect, actual results may differ materially from these estimates.

The integration of acquired businesses may present significant challenges to us.

In 2009 we acquired Proteolix, and in the future we may enter into other acquisitions of, or investments in, businesses, in order to complement or expand our current business or enter into a new product area. Achieving the anticipated benefits of any future acquisition, depends upon the successful integration of the acquired business' operations and personnel in a timely and efficient manner. The difficulties of integration include, among others:

consolidating research and development operations;

retaining key employees;

consolidating corporate and administrative infrastructures, including integrating and managing information technology and other support systems and processes;

preserving relationships with third parties, such as regulatory agencies, clinical investigators, key opinion leaders, clinical research organizations, contract manufacturing organizations, licensors and suppliers;

appropriately identifying and managing the liabilities of the combined company;

utilizing potential tax assets of the acquired business; and

managing risks associated with acquired facilities, including environmental risks and compliance with laws regulating laboratories.

We cannot assure stockholders that we will receive any benefits of any future merger or acquisition, or that any of the difficulties described above will not adversely affect us. In addition, integration efforts would place a significant burden on our management and internal resources, which

could result in delays in clinical trial and product development programs and otherwise harm our business, financial condition and operating results.

Negotiations associated with an acquisition or strategic investment could divert management's attention and other company resources. Any of the following risks associated with future acquisitions or investments could impair our ability to grow our business, develop new products, or sell Nexavar, Stivarga or Kyprolis, and ultimately could have a negative impact on our growth or our financial results for many reasons, including:

- difficulty in operating in a new or multiple new locations;
- difficulty in realizing the potential financial or strategic benefits of the transaction;
- difficulty in maintaining uniform standards, controls, procedures and policies;
- disruption of or delays in ongoing research, clinical trials and development efforts;
- diversion of capital and other resources;
- assumption of liabilities and unanticipated expenses resulting from litigation arising from potential or actual business acquisitions or investments; and
- difficulties in entering into new markets in which we have limited or no experience and where competitors in such markets have stronger positions.

In addition, the consideration for any future acquisition could be paid in cash, shares of our common stock, the issuance of convertible debt securities or a combination of cash, convertible debt and common stock. If we make an investment in cash or use cash to pay for all or a portion of an acquisition, our cash and investment balances would be reduced which could negatively impact our liquidity, the growth of our business or our ability to develop new products. However, if we pay the consideration with shares of common stock, or convertible debentures, the holdings of our existing stockholders could be diluted. We cannot forecast the number, timing or size of future strategic investments or acquisitions, or the effect that any such investments or acquisitions might have on our operations or financial results.

If we lose our key employees or are unable to attract or retain qualified personnel, our business could suffer.

The loss of the services of key employees may have an adverse impact on our business unless or until we hire a suitably qualified replacement. Any of our key personnel could terminate their employment with us at any time and without notice. We depend on our continued ability to attract, retain and motivate highly qualified personnel. We face competition for qualified individuals from numerous pharmaceutical and biotechnology companies, universities and other research institutions. In order to succeed in our research and development efforts, we will need to continue to hire individuals with the appropriate scientific skills.

We may need to further expand our sales, market access, managerial, operational, administrative and other functions in order to commercialize Kyprolis and/or Stivarga, manage and fund our operations and continue our development activities. To support this growth, we have hired and intend to continue hiring additional employees. Our management, personnel, systems and facilities currently in place may not be adequate to support this future growth. Our need to effectively manage our operations, growth and various projects requires that we:

Increase our activities related to commercialization, and effectively hire, train and manage a sales force, who will have limited or no prior experience with our company or our products, and establish appropriate systems, policies and infrastructure to support our commercial organization; and

continue to improve our operational, financial and management controls, reporting systems and procedures.

We may be unable to successfully implement these tasks on a larger scale and, accordingly, may not achieve our development and commercialization goals.

Risks associated with operating in foreign countries could materially adversely affect our business.

We have expanded our operations into Europe and, if approved in that region, we expect to import, market, sell and distribute our products in European countries. We currently maintain and expect to expand our presence in Europe. Our clinical and commercial supply chain activities could occur outside the United States. Consequently, we are, and will continue to be, subject to risks related to operating in foreign countries. Risks associated with conducting operations in foreign countries include:

differing regulatory requirements for drug approvals and regulation of approved drugs in foreign countries;

unexpected changes in tariffs, trade barriers and regulatory requirements;

economic weakness, including inflation, or political instability in particular foreign economies and markets;

compliance with tax, employment, immigration and labor laws for employees living or traveling abroad;

foreign taxes, including withholding of payroll taxes;

foreign currency fluctuations, which could result in increased operating expenses or reduced revenues, and other obligations incident to doing business or operating in another country;

workforce uncertainty in countries where labor unrest is more common than in the United States;

production shortages resulting from any events affecting raw material supply or manufacturing capabilities abroad; and

business interruptions resulting from geo-political actions, including war and terrorism.

These and other risks described elsewhere in these risk factors associated with our international operations could materially adversely affect our business.

We may be subject to claims that our employees have wrongfully used or disclosed alleged trade secrets of their former employers.

As is common in the biotechnology and pharmaceutical industries, we employ individuals who were previously employed at educational institutions or other biotechnology or pharmaceutical companies, including our competitors or potential competitors. Although no claims against us are currently pending, we may be subject to claims that these employees or we have inadvertently or otherwise used or disclosed trade secrets or other proprietary information of 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 be a distraction to management.

We incurred significant indebtedness through the sale of our 4.0% convertible senior notes due 2016, and we may incur additional indebtedness in the future. The indebtedness created by the sale of the notes and any future indebtedness we incur exposes us to risks that could adversely affect our business, financial condition and results of operations.

We incurred senior indebtedness in August 2009 when we sold $230 million aggregate principal amount of 4.0% convertible senior notes due 2016, or the 2016 Notes. We may also incur additional long-term indebtedness or obtain working capital lines of credit to meet future financing needs. Our indebtedness could have significant negative consequences for our business, results of operations and financial condition, including:

increasing our vulnerability to adverse economic and industry conditions;

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;

limiting our flexibility in planning for, or reacting to, changes in our business; 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 stockholders 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 2016 Notes, or any indebtedness which we may incur in the future, we would be in default, which would permit the holders of the 2016 Notes and such other indebtedness to accelerate the maturity of the notes and such other indebtedness and could cause defaults under the 2016 Notes and such other indebtedness. Any default under the notes or any indebtedness which we may incur in the future could have a material adverse effect on our business, results of operations and financial condition.

The conditional conversion features of the 2016 Notes were triggered on October 1, 2012 and again on January 1, 2013. The holders of the 2016 Notes are entitled to convert the 2016 Notes through March 31, 2013, at their option. If one or more holders elect to convert their 2016 Notes, unless we elect to satisfy our conversion obligation by delivering solely shares of our common stock, we would be required to make cash payments to satisfy all or a portion of our conversion obligation based on the applicable conversion rate, which could adversely affect our liquidity. In addition, even if holders do not elect to convert their 2016 Notes, we could be required under applicable accounting rules to reclassify all or a portion of the outstanding principal of the 2016 Notes as a current rather than long-term liability, which could result in a material reduction of our net working capital.

We face product liability risks and may not be able to obtain adequate insurance.

The sales of Nexavar, Stivarga and Kyprolis, and the use of Nexavar, Kyprolis, Stivarga and/or other products and product candidates in clinical trials expose us to product liability claims. In the United States, FDA approval of a drug may not offer protection from liability claims under state law (i.e., federal preemption defense), the tort duties for which may vary state to state. If we cannot successfully defend ourselves against product liability claims, we may incur substantial liabilities or be required to limit commercialization of Nexavar, Kyprolis, Stivarga and/or future products.

We may not be able to maintain product liability insurance coverage at a reasonable cost. We may not be able to obtain additional insurance coverage that will be adequate to cover product liability risks that may arise should a future product candidate receive marketing approval. Whether or not we are

insured, a product liability claim or product recall may result in significant losses. Regardless of merit or eventual outcome, product liability claims may result in:

decreased demand for a product;

injury to our reputation;

distraction of management;

withdrawal of clinical trial volunteers; and

loss of revenues.

We or Bayer may not be able to protect or enforce our or their intellectual property rights and we may not be able to operate our business without infringing the intellectual property rights of others.

We can protect our technology from unauthorized use by others only to the extent that our technology is covered by valid and enforceable patents, effectively maintained as trade secrets, or otherwise protected as confidential information or know-how. We depend in part on our ability to:

obtain patents;

license technology rights from others;

protect trade secrets;

operate without infringing upon the proprietary rights of others; and

prevent others from infringing on our proprietary rights, particularly generic drug manufacturers.

Patents and patent applications covering Nexavar and Stivarga are owned by Bayer. Those Nexavar patents that arose out of our collaboration agreement with Bayer are licensed to us, including two United States patents covering Nexavar and pharmaceutical compositions of Nexavar. Both patents will expire January 12, 2020. These two patents are listed in the FDA's Approved Drug Product List (Orange Book). Based on publicly available information, Bayer also has patents in several European countries covering Nexavar, which will expire in 2020. Bayer has other patents and patent applications pending worldwide that cover Nexavar alone or in combination with other drugs for treating cancer. Certain of these patents may be subject to possible patent-term extension, the entitlement to and the term of which cannot presently be calculated, in part because Bayer does not share with us information related to its Nexavar patent portfolio. We cannot be certain that Bayer's issued patents and future patents if they issue will provide adequate protection for Nexavar or Stivarga or will not be challenged by third parties in connection with the filing of an ANDA, or otherwise. Similarly, we cannot be certain that the patents and patent applications owned by us, acquired in the Proteolix acquisition, or licensed to us by any licensor, will provide adequate protection for Kyprolis or any other product, or will not be challenged by third parties in connection with the filing of an ANDA, or otherwise. The patents related to Kyprolis and oprozomib will begin to expire in 2025 and

2027, respectively. Third parties may claim to have rights in the assets that we acquired with Proteolix, including Kyprolis, or to have intellectual property rights that will be infringed by our commercialization of our assets, including those that we acquired with Proteolix. If third parties were to succeed in such claims, our business and company could be harmed.

The patent positions of biotechnology and pharmaceutical companies are highly uncertain and involve complex legal and factual questions. Our patents, or patents that we license from others, may not provide us with proprietary protection or competitive advantages against competitors with similar technologies. Competitors may challenge or circumvent our patents or patent applications. Courts may find our patents invalid. Due to the extensive time required for development, testing and regulatory

review of our potential products, our patents may expire or remain in existence for only a short period following commercialization, which would reduce or eliminate any advantage the patents may give us.

We may not have been the first to make the inventions covered by each of our issued or pending patent applications, or we may not have been the first to file patent applications for these inventions. Third party patents may cover the materials, methods of treatment or dosage related to our product, or compounds to be used in combination with our products; those third parties may make allegations of infringement. We cannot provide assurances that our products or activities, or those of our licensors or licensees, will not infringe patents or other intellectual property owned by third parties. Competitors may have independently developed technologies similar or complementary to ours, including compounds to be used in combination with our products. We may need to license the right to use third-party patents and intellectual property to develop and market our product candidates. We may be unable to acquire required licenses on acceptable terms, if at all. If we do not obtain these required licenses, we may need to design around other parties' patents, or we may not be able to proceed with the development, manufacture or, if approved, sale of our product candidates. We may face litigation to defend against claims of infringement or other violations of intellectual property rights, assert claims of infringement, enforce our patents, protect our trade secrets or know-how, or determine the scope and validity of others' proprietary rights. In addition, we may require interference or similar proceedings in the United States Patent and Trademark Office or its foreign counterparts to establish priority of invention. These activities are uncertain, making any outcome difficult to predict and costly and may be a substantial distraction for our management team.

Bayer may have rights to publish data and information in which we have rights. In addition, we sometimes engage individuals, entities or consultants, including clinical investigators, to conduct research that may be relevant to our business. The ability of these third parties to publish or otherwise publicly disclose information generated during the course of their research is subject to certain contractual limitations; however, these contracts may be breached and we may not have adequate remedies for any such breach. If we do not apply for patent protection prior to publication or if we cannot otherwise maintain the confidentiality of our confidential information, then our ability to receive patent protection or protect our proprietary information will be harmed.

In addition, on September 16, 2011, the Leahy-Smith America Invents Act, or the Leahy-Smith Act, was signed into law. The Leahy-Smith Act includes a number of significant changes to United States patent law. These include provisions that affect the way patent applications will be prosecuted and may also affect patent litigation. The United States Patent Office is currently developing regulations and procedures to govern administration of the Leahy-Smith Act, and many of the substantive changes to patent law associated with the Leahy-Smith Act have not yet become effective. Accordingly, it is not clear what, if any, impact the Leahy-Smith Act will have on the operation of our business. However, the Leahy-Smith Act, in particular the first-to-file provision, and its implementation could increase the uncertainties and costs surrounding the prosecution of our patent applications and the enforcement or defense of our issued patents, all of which could have a material adverse effect on our business and financial condition.

Limited foreign intellectual property protection and compulsory licensing could limit our revenue opportunities.

The laws of some foreign countries do not protect intellectual property rights to the same extent as the laws of the United States. The requirements for patentability may differ in certain countries, particularly developing countries. In 2009, we became aware that a third-party had filed an opposition proceeding with the Chinese patent office to invalidate the patent that covers Nexavar. Unlike other countries, China has a heightened requirement for patentability, and specifically requires a detailed description of medical uses of a claimed drug, such as Nexavar. The third party filed an appeal to the

Beijing No. 1 Court to which Bayer responded and the Court found in Bayer's favor. The appeal period for this decision has recently expired, and thus the Nexavar Chinese patent has been upheld.

Generic drug manufacturers or other competitors may challenge the scope, validity or enforceability of the Nexavar patents, requiring Bayer and us to engage in complex, lengthy and costly litigation or other proceedings. Generic drug manufacturers may develop, seek approval for, and launch generic versions of Nexavar. For example, Bayer has a patent in India that covers Nexavar. Cipla Limited, an Indian generic drug manufacturer, applied to the Drug Controller General of India, or DCGI, for market approval for Nexavar, which Bayer sought to block based on its patent. Bayer sued the DCGI and Cipla Limited in the Delhi High Court requesting an injunction to bar the DCGI from granting Cipla Limited market authorization. The Court ruled against Bayer, stating that in India, unlike the U.S., there is no link between regulatory approval of a drug and its patent status. Bayer unsuccessfully appealed. Consequently, Bayer has appealed to the Indian Supreme Court, and has filed a patent infringement suit against Cipla that is currently pending before the Delhi high court, Cipla, however, is now selling a generic version of Nexavar in India. Also, recently, India's controller general of patents, designs and trademarks has granted a compulsory license to the Indian generic drug manufacturer, Natco, to make a generic version of Nexavar, and Natco has commenced production of a generic version of Nexavar. Bayer has appealed this ruling, and has also sued Natco for patent infringement. The compulsory license granted to Natco does not give Natco the right to sell Nexavar outside of India. Two other Indian companies, MDL ChemPharm and BDR Pharmaceuticals Inc., have filed for a compulsory license to sell generic Nexavar. Bayer has sued both these parties for patent infringement.

In addition to India, certain countries in Europe and developing countries, including China, have compulsory licensing laws under which a patent owner may be compelled to grant licenses to third parties. In those countries, Bayer, the owner of the Nexavar patent estate, may have limited remedies if the Nexavar patents are infringed or if Bayer is compelled to grant a license for Nexavar to a third party, which could materially diminish the value of those patents that cover Nexavar. This could limit our potential revenue opportunities.

If we use hazardous or potentially hazardous materials in a manner that causes injury or violates applicable law, we may be liable for damages.

Our research and development activities involve the controlled use of hazardous or potentially hazardous materials, including chemical, biological and radioactive materials. In addition, our operations produce hazardous waste products. Federal, state and local laws and regulations govern the use, manufacture, storage, handling and disposal of hazardous materials. We may incur significant additional costs to comply with these and other applicable laws in the future. Also, even if we are in compliance with applicable laws, we cannot completely eliminate the risk of contamination or injury resulting from hazardous materials and we may incur liability as a result of any such contamination or injury. In the event of an accident, we could be held liable for damages or penalized with fines, and the liability could significantly deplete or even exhaust our resources. We do not have any insurance for liabilities arising from hazardous materials. Compliance with applicable environmental laws and regulations is expensive, and current or future environmental regulations may impair our research, development and manufacturing efforts, which could harm our business. We are subject to various laws and regulations governing laboratory practices and the experimental use of animals. We are also subject to regulation by the Occupational Safety and Health Administration, or OSHA, and the Environmental Protection Agency, or the EPA, and to regulation under the Toxic Substances Control Act, the Resource Conservation and Recovery Act and other regulatory statutes, and may in the future be subject to other federal, state or local regulations. OSHA and/or the EPA may promulgate regulations that may affect our research and development programs.

A portion of our investment portfolio is invested in auction rate securities, and if auctions continue to fail for amounts we have invested, our investment will not be liquid. If the issuer of an auction rate security that we hold is unable to successfully close future auctions and their credit rating deteriorates, we may be required to adjust the carrying value of our investment through an impairment charge to earnings.

Less than 3% of our investment portfolio is invested in auction rate securities. The underlying assets of these securities are student loans substantially backed by the federal government. Due to adverse developments in the credit markets, beginning in February 2008, these securities have experienced failures in the auction process. When an auction fails for amounts we have invested, the security becomes illiquid. In the event of an auction failure, we are not able to access these funds until a future auction on these securities is successful. We have classified these securities as non-current marketable securities, and if the issuer is unable to successfully close future auctions and their credit rating deteriorates, we may be required to adjust the carrying value of the marketable securities through an impairment charge to earnings.

Provisions in the indenture for the 2016 Notes may deter or prevent a business combination.

If a fundamental change occurs prior to the maturity date of the 2016 Notes, holders of the notes will have the right, at their option, to require us to repurchase all or a portion of their notes. In addition, if a fundamental change occurs prior to the maturity date of 2016 Notes, we will in some cases be required to increase the conversion rate for a holder that elects to convert its notes in connection with such fundamental change. A fundamental change is defined in the indenture governing the 2016 Notes and includes certain transactions resulting in a change of control of our common stock, the approval of a plan for our liquidation or dissolution or the delisting of our common stock from the NASDAQ or other national securities exchanges. In addition, the indenture for the notes prohibits us from engaging in certain mergers or acquisitions unless, among other things, the surviving entity assumes our obligations under the 2016 Notes. These and other provisions could prevent or deter a third party from acquiring us even where the acquisition could be beneficial to our stockholders.

Our business may be affected by other legal proceedings.

We have been in the past, and may become in the future, involved in legal proceedings, such as our lawsuit against Bayer regarding Stivarga and Nexavar. Civil and criminal litigation is inherently unpredictable and outcomes can result in significant fines, penalties and/or injunctive relief that could affect how we operate our business. Monitoring and defending against legal actions, whether or not meritorious, is time-consuming for our management and detracts from our ability to fully focus our internal resources on our business activities. In addition, legal fees and costs incurred in connection with such activities may be significant. We cannot predict with certainty the outcome of any legal proceedings in which we become involved and it is difficult to estimate the possible costs to us stemming from these matters. Settlements and decisions adverse to our interests in legal actions could result in the payment of substantial amounts and could have a material adverse effect on our cash flow, results of operations and financial position.

A breakdown or breach of our information technology systems could subject us to liability or interrupt the operation of our business.

We rely upon our information technology systems and infrastructure for our business. The size and complexity of our computer systems make them potentially vulnerable to breakdown, malicious intrusion and random attack. Likewise, data privacy breaches by employees and others who access our systems may pose a risk that sensitive data may be exposed to unauthorized persons or to the public. There can be no assurance that our management or diligence efforts will prevent breakdowns or breaches in our systems that could adversely affect our business.

Provisions in Delaware law, our charter and executive change of control agreements we have entered into may prevent or delay a change of control.

Certain provisions of our certificate of incorporation and bylaws, as well as provisions of the Delaware General Corporation Law, may have the effect of delaying, deferring or preventing a change in control of us, including transactions in which our stockholders might otherwise have received a substantial premium for their shares over then current market prices. For examples, these provisions:

- give authority to our board of directors to issue preferred stock and to determine the price, rights, preferences, privileges and restrictions of those shares without any stockholder vote;
- provide for a board of directors consisting of three classes, each of which serves for a different three-year term and do not provide for cumulative voting in the election of directors;
- provide that stockholders may only act at a duly called meeting of stockholders and not by written consent;
- allow special meetings of the stockholders to be called only by the chairman of the board, the chief executive officer, the board or 10% or more of the stockholders entitled to vote at the meeting;
- require stockholders to give advance notice prior to submitting proposals for consideration at stockholders' meetings or to nominate persons for election as directors; and
- restrict certain business combinations between us and any person who beneficially owns 15% or more of our outstanding voting stock.

We have entered into change in control severance agreements with each of our executive officers. These agreements provide for the payment of severance benefits and the acceleration of stock option vesting if the executive officer's employment is terminated within 24 months of a change in control. The change in control severance agreements may have the effect of preventing a change in control.

In the future, the failure of one or more of our customers could have a significant impact on our business.

Following the commercial launch of Kyprolis, we a portion of our sales and trade accounts receivable arise from its sales in the United States and are primarily with a limited number of drug wholesalers and specialty distributors. As a result, we are highly dependent on these customers. This concentration of credit risk could increase the risk of financial loss, should one or more of these companies fail. Although we will monitor the financial performance and creditworthiness of our customers and will monitor economic conditions along with associated impacts on the financial markets and its business, there can be no assurance that our efforts will prevent credit losses that could adversely affect our business.

USE OF PROCEEDS

We estimate that the net proceeds from the sale of shares of common stock in this offering, after deducting underwriting discounts and estimated offering expenses payable by us, will be approximately $ million (or $ if the underwriters exercise in full their option to purchase additional shares). These numbers are based on the offering price to the public of $ per share.

We intend to use the net proceeds from this offering to fund our clinical development program for carfilzomib and oprozomib, and for other research and development activities, both ongoing and planned, as well as sales and marketing activities to commercialize Kyprolis around the world, and for general corporate purposes, including working capital. We may also use a portion of our net proceeds from these offerings to make potential milestone payments to the Proteolix shareholders; to pay a portion of or all of our $230 million convertible debt when due; to further build and diversify our pipeline by in-licensing products or product candidates or investing in or acquiring businesses or technologies that we believe are complementary to our own. We have no current commitments or agreements with respect to any such transactions. We have not determined the amounts we plan to spend on any of the areas listed above or the timing of these expenditures. As a result, our management will have broad discretion to allocate the net proceeds of these offerings. Pending the application of the net proceeds from these offerings, we expect to invest the proceeds in investment-grade, interest-bearing securities.

The 4.0% convertible senior notes due 2016, or the 2016 Notes, were issued in August 2009 and bear interest at a rate of 4.00% per year, payable semi-annually in arrears, on February 15 and August 15 of each year, commencing on February 15, 2010. The 2016 Notes mature on August 15, 2016, unless earlier converted, repurchased or redeemed.

DIVIDEND POLICY

We have never declared or paid any cash dividends on our common stock and we do not anticipate paying cash dividends in the foreseeable future. We currently intend to retain our earnings, if any, for future growth. Future dividends on our common stock, if any, will be at the discretion of our Board of Directors and will depend on, among other things, our operations, capital requirements and surplus, general financial condition, contractual restrictions and such other factors that our Board of Directors may deem relevant.

DESCRIPTION OF CAPITAL STOCK

As of the date of this prospectus supplement, our authorized capital stock consists of 200,000,000 shares of common stock, par value $0.001 per share and 5,000,000 shares of preferred stock, par value $0.001 per share. As of December 31, 2012, there were 67,444,506 shares of common stock outstanding and no shares of preferred stock outstanding.

The following summary description of our capital stock is based on the provisions of our certificate of incorporation and bylaws and the applicable provisions of the Delaware General Corporation Law, or the DGCL. This information is qualified entirely by reference to the applicable provisions of our amended and restated certificate of incorporation, amended and restated bylaws and the DGCL. For information on how to obtain copies of our certificate of incorporation and bylaws, see "Where You Can Find More Information."

Common Stock

The holders of our common stock are entitled to one vote for each share held of record on all matters submitted to a vote of the stockholders. The holders of common stock are not entitled to cumulative voting rights with respect to the election of directors, and as a consequence, minority stockholders will not be able to elect directors on the basis of their votes alone.

Subject to preferences that may be applicable to any then outstanding shares of preferred stock, holders of common stock are entitled to receive ratably such dividends as may be declared by the Board of Directors out of funds legally available therefor. In the event of a liquidation, dissolution or winding up of us, holders of the common stock are entitled to share ratably in all assets remaining after payment of liabilities and the liquidation preferences of any then outstanding shares of preferred stock. Holders of common stock have no preemptive rights and no right to convert their common stock into any other securities. There are no redemption or sinking fund provisions applicable to our common stock. All outstanding shares of common stock are fully paid and non-assessable.

Preferred Stock

Our amended and restated certificate of incorporation provides that our Board of Directors has the authority, without further action by the stockholders, to issue up to 5,000,000 shares of preferred stock in one or more series and to fix the rights, preferences, privileges and restrictions of this preferred stock, including dividend rights, conversion rights, voting rights, terms of redemption, liquidation preferences, sinking fund terms and the number of shares constituting any series or the designation of a series, without further vote or action by the stockholders. Any preferred stock so issued by the Board of Directors may rank senior to the common stock with respect to the payment of dividends or amounts upon liquidation, dissolution or winding up of the company, or both. In addition, any such shares of preferred stock may have class or series voting rights. Moreover, under certain circumstances, the issuance of preferred stock or the existence of the unissued preferred stock might tend to discourage or render more difficult a merger or other change in control of us. We have no present plan to issue any shares of preferred stock.

Anti-Takeover Effects of Provisions of Delaware Law and Our Charter Documents

Certain provisions of Delaware law and our amended and restated certificate of incorporation and amended and restated bylaws could make more difficult the acquisition of us by means of a tender offer, a proxy contest, or otherwise, and the removal of incumbent officers and directors. These provisions are expected to discourage certain types of coercive takeover practices and inadequate takeover bids and to encourage persons seeking to acquire control of us to first negotiate with us. We believe that the benefits of increased protection of our potential ability to negotiate with the proponent of an unfriendly or unsolicited proposal to acquire or restructure us outweighs the disadvantages of

discouraging such proposals, including proposals that are priced above the then current market value of our common stock, because, among other things, negotiation of such proposals could result in an improvement of their terms.

Delaware Takeover Statute. We are subject to section 203 of the DGCL. This provision generally prohibits a Delaware corporation from engaging in any business combination with any interested stockholder for a period of three years following the date such stockholder became an interested stockholder, unless:

- prior to such date the board of directors of the corporation approved either the business combination or the transaction that resulted in the stockholder becoming an interested stockholder;

- upon consummation of the transaction that resulted in the stockholder becoming an interested stockholder, the interested stockholder owned at least 85% of the voting stock of the corporation outstanding at the time the transaction commenced, excluding for purposes of determining the number of shares outstanding those shares owned by persons who are directors and also officers and by employee stock plans in which employee participants do not have the right to determine confidentially whether shares held subject to the plan will be tendered in a tender or exchange offer; or

- on or subsequent to such date, the business combination is approved by the board of directors and authorized at an annual or special meeting of stockholders, and not by written consent, by the affirmative vote of at least $66^{2}/_{3}\%$ of the outstanding voting stock that is not owned by the interested stockholder.

Section 203 defines business combination to include:

- any merger or consolidation involving the corporation and the interested stockholder;

- any sale, transfer, pledge or other disposition of 10% or more of the assets of the corporation involving the interested stockholder;

- subject to certain exceptions, any transaction that results in the issuance or transfer by the corporation of any stock of the corporation to the interested stockholder;

- any transaction involving the corporation that has the effect of increasing the proportionate share of the stock of any class or series of the corporation beneficially owned by the interested stockholder; or the receipt by the interested stockholder of the benefit of any loans, advances, guarantees, pledges or other financial benefits provided by or through the corporation.

In general, section 203 defines an interested stockholder as any entity or person beneficially owning 15% or more of the outstanding voting stock of the corporation and any entity or person affiliated with or controlling or controlled by such entity or person.

Charter Documents. Our amended and restated certificate of incorporation provides:

- for a board of directors, classified into three classes of directors as nearly equal in size as possible with staggered terms;

- for the authority of our board to issue up to 5,000,000 shares of preferred stock and to determine the price, rights, preferences and privileges of these shares, without stockholder approval;

that any action required or permitted to be taken by our stockholders must be effected at a duly called annual or special meeting of stockholders and may not be effected by a consent in writing;

that special meetings of the stockholders may be called only by the chairman of the board, president, the board of directors pursuant to a resolution adopted by a majority of the total number of authorized directors, or by the holders of the shares entitled to cast not less than ten percent (10%) of the votes at the meeting; and

for no cumulative voting.

These and other provisions contained in our amended and restated certificate of incorporation and amended and restated bylaws could delay or discourage some types of transactions involving an actual or potential change in our control or change in our management, including transactions in which stockholders might otherwise receive a premium for their shares over then current prices, and may limit the ability of stockholders to remove current management or approve transactions that stockholders may deem to be in their best interests and, therefore, could adversely affect the price of our common stock.

Limitation on Liability and Indemnification of Officers and Directors

Section 145(a) of the DGCL provides in relevant part that "[a] corporation shall have power to indemnify any person who was or is a party or is threatened to be made a party to any threatened, pending or completed action, suit or proceeding, whether civil, criminal, administrative or investigative (other than an action by or in the right of the corporation) by reason of the fact that the person is or was a director, officer, employee or agent of the corporation, or is or was serving at the request of the corporation as a director, officer, employee or agent of another corporation, partnership, joint venture, trust or other enterprise, against expenses (including attorneys' fees), judgments, fines and amounts paid in settlement actually and reasonably incurred by the person in connection with such action, suit or proceeding if the person acted in good faith and in a manner the person reasonably believed to be in or not opposed to the best interests of the corporation, and, with respect to any criminal action or proceeding, had no reasonable cause to believe the person's conduct was unlawful." With respect to derivative actions, Section 145(b) of the DGCL provides in relevant part that "[a] corporation shall have power to indemnify any person who was or is a party or is threatened to be made a party to any threatened, pending or completed action or suit by or in the right of the corporation to procure a judgment in its favor...[by reason of the person's service in one of the capacities specified in the preceding sentence] against expenses (including attorneys' fees) actually and reasonably incurred by the person in connection with the defense or settlement of such action or suit if the person acted in good faith and in a manner the person reasonably believed to be in or not opposed to the best interests of the corporation and except that no indemnification shall be made in respect of any claim, issue or matter as to which such person shall have been adjudged to be liable to the corporation unless and only to the extent that the Court of Chancery or the court in which such action or suit was brought shall determine upon application that, despite the adjudication of liability but in view of all the circumstances of the case, such person is fairly and reasonably entitled to indemnity for such expenses which the Court of Chancery or such other court shall deem proper."

Our amended and restated certificate of incorporation provides that to the fullest extent permitted by the DGCL, none of our directors shall be personally liable to us or our stockholders for monetary damages for breach of fiduciary duty as a director. The amended and restated certificate of incorporation also provides that no amendment or repeal of such provision shall apply to or have any effect on the right to indemnification permitted thereunder with respect to claims arising from acts or omissions occurring in whole or in part before the effective date of such amendment or repeal whether asserted before or after such amendment or repeal.

Our amended and restated bylaws provide for the indemnification of directors and officers to the fullest extent no prohibited by the DGCL and that the Company shall have the power to indemnify its employees and other agents as set forth in the DGCL. We have entered into indemnification

agreements with our directors and executive officers and intend to enter into indemnification agreements with any new directors and executive officers in the future.

We also carry officer and director liability insurance with respect to certain matters, including matters arising under the Securities Act.

Transfer Agent and Registrar

The transfer agent and registrar for our common stock is Wells Fargo Bank, N.A. Its address is Shareholder Services, 161 North Concord Exchange, South St. Paul, Minnesota 55075 and its telephone number is (800) 468-9716.

MATERIAL U.S. FEDERAL INCOME TAX CONSEQUENCES TO NON-U.S. HOLDERS OF OUR COMMON STOCK

The following summary describes the material U.S. federal income tax consequences of the acquisition, ownership and disposition of our common stock acquired in this offering by Non-U.S. Holders (as defined below). This discussion does not address all aspects of U.S. federal income taxes and does not deal with state, local or non-U.S. tax consequences that may be relevant to Non-U.S. Holders in light of their particular circumstances, nor does it address U.S. federal tax consequences other than income taxes. Special rules different from those described below may apply to certain Non-U.S. Holders that are subject to special treatment under the Internal Revenue Code of 1986, as amended, or the Code, such as financial institutions, insurance companies, tax-exempt organizations, broker-dealers and traders in securities, U.S. expatriates, "controlled foreign corporations," "passive foreign investment companies," corporations that accumulate earnings to avoid U.S. federal income tax, persons that hold our common stock as part of a "straddle," "hedge," "conversion transaction," "synthetic security" or integrated investment or other risk reduction strategy, partnerships and other pass-through entities, and investors in such pass-through entities or entities that are treated as disregarded entities for U.S. federal income tax purposes (regardless of their places of organization or formation). Such Non-U.S. Holders are urged to consult their own tax advisors to determine the U.S. federal, state, local and other tax consequences that may be relevant to them. Furthermore, the discussion below is based upon the provisions of the Code, and Treasury regulations, rulings and judicial decisions thereunder as of the date hereof, and such authorities may be repealed, revoked or modified, perhaps retroactively, so as to result in U.S. federal income tax consequences different from those discussed below. We have not requested a ruling from the IRS with respect to the statements made and the conclusions reached in the following summary, and there can be no assurance that the IRS will agree with such statements and conclusions. This discussion assumes that the Non-U.S. Holder holds our common stock as a "capital asset" within the meaning of Section 1221 of the Code (generally, property held for investment).

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

For the purposes of this discussion, a "Non-U.S. Holder" is, for U.S. federal income tax purposes, a beneficial owner of common stock that is not a U.S. Holder. A "U.S. Holder" means a beneficial owner of our common stock that is for U.S. federal income tax purposes (a) an individual who is a citizen or resident of the United States, (b) a corporation or other entity treated as a corporation created or organized in or under the laws of the United States, any state thereof or the District of Columbia, (c) an estate the income of which is subject to U.S. federal income taxation regardless of its source or (d) a trust if it (1) is subject to the primary supervision of a court within the United States and one or more U.S. persons have the authority to control all substantial decisions of the trust or (2) has a valid election in effect under applicable U.S. Treasury regulations to be treated as a U.S. person. Also, partnerships, or other entities that are treated as partnerships for U.S. federal income tax purposes (regardless of their place of organization or formation) and entities that are treated as disregarded entities for U.S. federal income tax purposes (regardless of their place of organization or formation) are not addressed by this discussion and are, therefore, not considered to be Non-U.S. Holders for the purposes of this discussion.

Distributions

Subject to the discussion below, distributions, if any, made on our common stock to a Non-U.S. Holder of our common stock to the extent made out of our current or accumulated earnings and profits (as determined under U.S. federal income tax principles) generally will constitute dividends for U.S. tax purposes and will be subject to withholding tax at a 30% rate or such lower rate as may be specified by an applicable income tax treaty. To obtain a reduced rate of withholding under a treaty, a Non-U.S. Holder generally will be required to provide us with a properly executed IRS Form W-8BEN, or other appropriate form, certifying the Non-U.S. Holder's entitlement to benefits under that treaty. In the case of a Non-U.S. Holder that is an entity, Treasury Regulations and the relevant tax treaty provide rules to determine whether, for purposes of determining the applicability of a tax treaty, dividends will be treated as paid to the entity or to those holding an interest in that entity. If a Non-U.S. Holder holds stock through a financial institution or other agent acting on the holder's behalf, the holder will be required to provide appropriate documentation to such agent. The holder's agent will then be required to provide certification to us or our paying agent, either directly or through other intermediaries. If you are eligible for a reduced rate of U.S. federal withholding tax under an income tax treaty, you should consult with your own tax advisor to determine if you are able to obtain a refund or credit of any excess amounts withheld by timely filing an appropriate claim for a refund with the IRS.

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

To the extent distributions on our common stock, if any, exceed our current and accumulated earnings and profits, they will first reduce your adjusted basis in our common stock as a non-taxable return of capital, but not below zero, and then any excess will be treated as gain and taxed in the same manner as gain realized from a sale or other disposition of common stock as described in the next section.

Gain on Disposition of Our Common Stock

Subject to the discussion below regarding backup withholding and foreign accounts, a Non-U.S. Holder generally will not be subject to U.S. federal income tax with respect to gain realized on a sale or other disposition of our common stock unless (a) the gain is effectively connected with a trade or business of such holder in the United States (and, if required by an applicable income tax treaty, is attributable to a permanent establishment that such holder maintains in the United States), (b) the Non-U.S. Holder is a nonresident alien individual and is present in the United States for 183 or more days in the taxable year of the disposition and certain other conditions are met, or (c) we are or have been a "United States real property holding corporation" within the meaning of Code Section 897(c)(2) at any time within the shorter of the five-year period preceding such disposition or such holder's holding period.

If you are a Non-U.S. Holder described in (a) above, you will be required to pay tax on the net gain derived from the sale at regular graduated U.S. federal income tax rates, unless a specific treaty exemption applies, and corporate Non-U.S. Holders described in (a) above may be subject to the additional branch profits tax at a 30% rate or such lower rate as may be specified by an applicable income tax treaty. If you are an individual Non-U.S. Holder described in (b) above, you will be required to pay a flat 30% tax on the gain derived from the sale, which gain may be offset by U.S. source capital losses (even though you are not considered a resident of the United States). With respect to (c) above, in general, we would be a United States real property holding corporation if interests in U.S. real estate comprised (by fair market value) at least half of our assets. We believe that we are not, and do not anticipate becoming, a United States real property holding corporation, however, there can be no assurance that we will not become a U.S. real property holding corporation in the future. Even if we are treated as a U.S. real property holding corporation, gain realized by a Non-U.S. Holder on a disposition of our common stock will not be subject to U.S. federal income tax so long as (1) the Non-U.S. Holder owned, directly, indirectly and constructively, no more than five percent of our common stock at all times within the shorter of (i) the five-year period preceding the disposition or (ii) the holder's holding period and (2) our common stock is regularly traded on an established securities market. There can be no assurance that our common stock will continue to qualify as regularly traded on an established securities market.

Information Reporting Requirements and Backup Withholding

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

Dividends paid by us (or our paying agents) to a Non-U.S. Holder may also be subject to U.S. backup withholding. U.S. backup withholding generally will not apply to a Non-U.S. Holder who provides a properly executed IRS Form W-8BEN or otherwise establishes an exemption.

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

If backup withholding is applied to you, you should consult with your own tax advisor to determine if you are able to obtain a tax benefit or credit with respect to such backup withholding.

Foreign Accounts

A U.S. federal withholding tax of 30% may apply on dividends and the gross proceeds of a disposition of our common stock paid to a foreign financial institution (as specifically defined by applicable rules) unless such institution enters into an agreement with the U.S. government to withhold on certain payments and to collect and provide to the U.S. tax authorities substantial information

regarding U.S. account holders of such institution (which includes certain equity holders of such institution, as well as certain account holders that are foreign entities with U.S. owners). This U.S. federal withholding tax of 30% will also apply on dividends and the gross proceeds of a disposition of our common stock paid to a non-financial foreign entity unless such entity provides the withholding agent with either a certification that it does not have any substantial direct or indirect U.S. owners or provides information regarding direct and indirect U.S. owners of the entity. The withholding tax described above will not apply if the foreign financial institution or non-financial foreign entity otherwise qualifies for an exemption from the rules. Under certain circumstances, a Non-U.S. Holder might be eligible for refunds or credits of such taxes. Holders are encouraged to consult with their own tax advisors regarding the possible implications of the legislation on their investment in our common stock.

Although these rules currently apply to applicable payments made after December 31, 2012, the IRS has issued guidance providing that the withholding provisions described above will generally apply to payments of dividends made on or after January 1, 2014 and to payments of gross proceeds from a sale or other disposition of common stock on or after January 1, 2017.

THE PRECEDING DISCUSSION OF MATERIAL U.S. FEDERAL INCOME TAX CONSIDERATIONS IS FOR GENERAL INFORMATION ONLY. IT IS NOT TAX ADVICE. EACH PROSPECTIVE INVESTOR SHOULD CONSULT ITS OWN TAX ADVISOR REGARDING THE TAX CONSEQUENCES OF PURCHASING, HOLDING AND DISPOSING OF OUR COMMON STOCK, INCLUDING THE CONSEQUENCES OF ANY PROPOSED CHANGE IN APPLICABLE LAW, AS WELL AS TAX CONSEQUENCES ARISING UNDER ANY STATE, LOCAL, NON-U.S. OR U.S. FEDERAL NON-INCOME TAX LAWS.

UNDERWRITING

Onyx and the underwriters for the offering named below have entered into an underwriting agreement with respect to the shares being offered. Subject to certain conditions, each underwriter has severally agreed to purchase the number of shares indicated in the following table.

Underwriters	Number of Shares
Merrill Lynch, Pierce, Fenner & Smith Incorporated	
Barclays Capital Inc.	
Total	

The underwriters are committed to take and pay for all of the shares being offered, if any are taken, other than the shares covered by the option described below unless and until this option is exercised.

If the underwriters sell more shares than the total number set forth in the table above, the underwriters have an option to buy up to an additional shares from the company to cover such sales. They may exercise that option for 30 days. If any shares are purchased pursuant to this option, the underwriters will severally purchase shares in approximately the same proportion as set forth in the table above.

The following table shows the per share and total underwriting discounts and commissions to be paid to the underwriters by the company. Such amounts are shown assuming both no exercise and full exercise of the underwriters' option to purchase additional shares.

	No Exercise	Full Exercise
Per Share	$	$
Total	$	$

Shares sold by the underwriters to the public will initially be offered at the public offering price set forth on the cover of this prospectus. Any shares sold by the underwriters to securities dealers may be sold at a discount of up to $ per share from the public offering price. If all the shares are not sold at the public offering price, the representatives may change the offering price and the other selling terms. The offering of the shares by the underwriters is subject to receipt and acceptance and subject to the underwriters' right to reject any order in whole or in part.

We and our directors and executive officers have agreed that, during the period beginning on the date hereof and continuing until the date 60 days after the date of this prospectus supplement, and subject to limited exceptions, neither we nor they will, without the prior consent of the underwriters, offer, pledge, sell or otherwise dispose of (or enter into any agreement to offer, pledge, sell or otherwise dispose of), directly or indirectly, any shares of common stock, any securities substantially similar to the common stock or any securities convertible into or exchangeable for, shares of common stock or substantially similar securities, or enter into any swap or other arrangement that transfers to another, in whole or in part, any of the economic consequences of ownership of the common stock or substantially similar securities.

With respect to us, the foregoing paragraph shall not apply to (i) issuances of shares of common stock pursuant to employee stock option plans existing on, or upon the conversion or exchange of convertible or exchangeable securities outstanding as of, the date hereof, (ii) the sale and issuance of the common stock in this offering, (iii) the issuance of common stock upon the conversion of the 2016 Notes and (iv) any agreement providing for the contingent future issuance of shares of common upon achievement of specified technical or financial milestones, *provided* that no shares of common stock shall be issuable pursuant to any such agreement until at least 60 days after the date hereof.

With respect to our directors and executive officers, the foregoing paragraph shall not apply to (i) transfers of common stock as a bona fide gift or gifts or by will or intestacy, provided that each donee, transferee or distributee thereof agrees to be bound in writing by the restrictions, (ii) transfers of common stock to any trust for the direct or indirect benefit of such individual or the immediate family of such individual, provided that the trustee of the trust agrees to be bound in writing by the restrictions, and provided further that any such transfer shall not involve a disposition for value, (iii) shares of common stock sold or tendered to us or withheld by us for tax withholding purposes in connection with the vesting of equity awards that are subject to a taxable event upon vesting, (iv) shares of common stock sold pursuant to a written contract, instruction or plan complying with Rule 10b5-1 under the Exchange Act, provided that such plan has been entered into prior to the date hereof and is not amended or modified during the 60-day restricted period or (v) transfers of common stock with the prior written consent of the underwriters on behalf of the underwriters.

The company and the selling stockholders have agreed to indemnify the several underwriters against certain liabilities, including liabilities under the Securities Act of 1933.

The company estimates that its share of the total expenses of the offering, excluding underwriting discounts and commissions, will be approximately $500,000.

In connection with the offering, the underwriters may purchase and sell shares of common stock in the open market. These transactions may include short sales, stabilizing transactions and purchases to cover positions created by short sales. Short sales involve the sale by the underwriters of a greater number of shares than they are required to purchase in the offering. "Covered" short sales are sales made in an amount not greater than the underwriters' option to purchase additional shares from the company in the offering. The underwriters may close out any covered short position by either exercising their option to purchase additional shares or purchasing shares in the open market. In determining the source of shares to close out the covered short position, the underwriters will consider, among other things, the price of shares available for purchase in the open market as compared to the price at which they may purchase additional shares pursuant to the option granted to them. "Naked" short sales are any sales in excess of such option. The underwriters must close out any naked short position by purchasing shares in the open market. A naked short position is more likely to be created if the underwriters are concerned that there may be downward pressure on the price of the common stock in the open market after pricing that could adversely affect investors who purchase in the offering. Stabilizing transactions consist of various bids for or purchases of common stock made by the underwriters in the open market prior to the completion of the offering.

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

Purchases to cover a short position and stabilizing transactions, as well as other purchases by the underwriters for their own accounts, may have the effect of preventing or retarding a decline in the market price of the company's stock, and together with the imposition of the penalty bid, may stabilize, maintain or otherwise affect the market price of the common stock. As a result, the price of the common stock may be higher than the price that otherwise might exist in the open market. If these activities are commenced, they may be discontinued at any time. These transactions may be effected on the NASDAQ Global Select Market, in the over-the-counter market or otherwise.

Certain of the underwriters and their respective affiliates have, from time to time, performed, and may in the future perform, various financial advisory and investment banking services for the company, for which they received or will receive customary fees and expenses. The underwriters may, from time to time in the future, engage in transactions with and perform services for us in the ordinary course of their business.

In the ordinary course of their various business activities, the underwriters and their respective affiliates may make or hold a broad array of investments and actively trade debt and equity securities (or related derivative securities) and financial instruments (including bank loans) for their own account and for the accounts of their customers, and such investment and securities activities may involve securities and/or instruments of the issuer. For instance, Barclays Capital Inc. or its affiliates hold positions in our outstanding convertible senior notes due 2016, and may receive a portion of the net proceeds from the sale of the notes through the conversion of such notes. The underwriters and their respective affiliates may also make investment recommendations and/or publish or express independent research views in respect of such securities or instruments and may at any time hold, or recommend to clients that they acquire, long and/or short positions in such securities and instruments.

William. R. Ringo, an independent director on our board, is a senior advisor, on matters unrelated to this offering, to Barclays Capital Inc. We do not believe that his interest as an advisor to Barclays Capital Inc. will conflict with your interest as purchasers of the common stock.

Selling Restrictions

European Economic Area

In relation to each Member State of the European Economic Area which has implemented the Prospectus Directive (each, a "Relevant Member State"), an offer to the public of any ordinary shares which are the subject of the offering contemplated by this prospectus supplement (the "Shares") may not be made in that Relevant Member State, except that an offer to the public in that Relevant Member State of any Shares may be made at any time under the following exemptions under the Prospectus Directive, if they have been implemented in that Relevant Member State:

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

b) to fewer than 100 or, if the Relevant Member State has implemented the relevant provision of the 2010 PD Amending Directive, 150, natural or legal persons (other than qualified investors as defined in the Prospectus Directive), as permitted under the Prospectus Directive, subject to obtaining the prior consent of the representative for any such offer; or

c) in any other circumstances falling within Article 3(2) of the Prospectus Directive, provided that no such offer of Shares shall result in a requirement for the publication by us or any underwriter of a prospectus pursuant to Article 3 of the Prospectus Directive.

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

United Kingdom

Each underwriter has represented and agreed that:

a) it has only communicated or caused to be communicated and will only communicate or cause to be communicated an invitation or inducement to engage in investment activity (within the meaning of Section 21 of the Financial Services and Market Act (the "FSMA")) received by it in connection

with the issue or sale of the ordinary shares in circumstances in which Section 21(1) of the FSMA does not apply to us; and

b) it has complied and will comply with all applicable provisions of the FSMA with respect to anything done by it in relation to the ordinary shares in, from or otherwise involving the United Kingdom.

Australia

This prospectus supplement has not been lodged with the Australian Securities & Investments Commission and does not constitute an offer except to the following categories of exempt persons:

a) "sophisticated investors" under section 708(8)(a) or (b) of the Corporations Act 2001 (Cth) of Australia ("Corporations Act");

b) "sophisticated investors" under section 708(8)(c) or (d) of the Corporations Act who have provided an accountant's certificate to us which complies with the requirements of section 708(8)(c)(i) or (ii) of the Corporations Act and related regulations before any offer has been made; and

c) "professional investors" within the meaning of section 708(11)(a) or (b) of the Corporations Act.

By purchasing ordinary shares, you warrant and agree that:

a) you are an exempt investor under one of the above categories; and

b) you will not offer any ordinary shares issued or sold to you pursuant to this document for sale in Australia within 12 months of those ordinary shares being issued or sold unless any such sale offer is exempt from the requirement to issue a disclosure document under sections 708 or 708A of the Corporations Act.

Hong Kong

The ordinary shares may not be offered or sold by means of any document other than (i) in circumstances which do not constitute an offer to the public within the meaning of the Companies Ordinance (Cap.32, Laws of Hong Kong), (ii) to "professional investors" within the meaning of the Securities and Futures Ordinance (Cap.571, Laws of Hong Kong) and any rules made thereunder, or (iii) in other circumstances which do not result in the document being a "prospectus" within the meaning of the Companies Ordinance (Cap.32, Laws of Hong Kong), and no advertisement, invitation or document relating to the ordinary shares may be issued or may be in the possession of any person for the purpose of issue (in each case whether in Hong Kong or elsewhere), which is directed at, or the contents of which are likely to be accessed or read by, the public in Hong Kong (except if permitted to do so under the laws of Hong Kong) other than with respect to ordinary shares which are or are intended to be disposed of only to persons outside Hong Kong or only to "professional investors" within the meaning of the Securities and Futures Ordinance (Cap. 571, Laws of Hong Kong) and any rules made thereunder.

India

This prospectus supplement has not been and will not be registered as a prospectus with the Registrar of Companies in India or with the Securities and Exchange Board of India. This prospectus supplement or any other material relating to these securities is for information purposes only and may not be circulated or distributed, directly or indirectly, to the public or any members of the public in India and in any event to not more than 50 persons in India. Further, persons into whose possession this prospectus supplement comes are required to inform themselves about and to observe any such restrictions. Each prospective investor is advised to consult its advisors about the particular

consequences to it of an investment in these securities. Each prospective investor is also advised that any investment in these securities by it is subject to the regulations prescribed by the Reserve Bank of India and the Foreign Exchange Management Act and any regulations framed thereunder.

Japan

The ordinary shares have not been and will not be registered under the Financial Instruments and Exchange Law of Japan (the "Financial Instruments and Exchange Law") and each underwriter has agreed that it will not offer or sell any ordinary shares, directly or indirectly, in Japan or to, or for the benefit of, any resident of Japan (which term as used herein means any person resident in Japan, including any corporation or other entity organized under the laws of Japan), or to others for re-offering or resale, directly or indirectly, in Japan or to a resident of Japan, except pursuant to an exemption from the registration requirements of, and otherwise in compliance with, the Financial Instruments and Exchange Law and any other applicable laws, regulations and ministerial guidelines of Japan.

Korea

The ordinary shares may not be offered, sold and delivered directly or indirectly, or offered or sold to any person for reoffering or resale, directly or indirectly, in Korea or to any resident of Korea except pursuant to the applicable laws and regulations of Korea, including the Korea Securities and Exchange Act and the Foreign Exchange Transaction Law and the decrees and regulations thereunder. The ordinary shares have not been registered with the Financial Services Commission of Korea for public offering in Korea. Furthermore, the ordinary shares may not be resold to Korean residents unless the purchaser of the ordinary shares complies with all applicable regulatory requirements (including but not limited to government approval requirements under the Foreign Exchange Transaction Law and its subordinate decrees and regulations) in connection with the purchase of the ordinary shares.

Singapore

This prospectus supplement has not been registered as a prospectus with the Monetary Authority of Singapore. Accordingly, this prospectus supplement and any other document or material in connection with the offer or sale, or invitation for subscription or purchase, of the ordinary shares may not be circulated or distributed, nor may the ordinary shares be offered or sold, or be made the subject of an invitation for subscription or purchase, whether directly or indirectly, to persons in Singapore other than (i) to an institutional investor under Section 274 of the Securities and Futures Act, Chapter 289 of Singapore (the "SFA"), (ii) to a relevant person, or any person pursuant to Section 275(1A), and in accordance with the conditions, specified in Section 275 of the SFA or (iii) otherwise pursuant to, and in accordance with the conditions of, any other applicable provision of the SFA.

Where the ordinary shares are subscribed or purchased under Section 275 by a relevant person which is: (a) a corporation (which is not an accredited investor) the sole business of which is to hold investments and the entire share capital of which is owned by one or more individuals, each of whom is an accredited investor; or (b) a trust (where the trustee is not an accredited investor) whose sole purpose is to hold investments and each beneficiary is an accredited investor, shares, debentures and units of shares and debentures of that corporation or the beneficiaries' rights and interest in that trust shall not be transferable for 6 months after that corporation or that trust has acquired the ordinary shares under Section 275 except: (1) to an institutional investor under Section 274 of the SFA or to a relevant person, or any person pursuant to Section 275(1A), and in accordance with the conditions, specified in Section 275 of the SFA; (2) where no consideration is given for the transfer; or (3) by operation of law.

Switzerland

The shares may not be publicly offered in Switzerland and will not be listed on the SIX Swiss Exchange ("SIX") or on any other stock exchange or regulated trading facility in Switzerland. This document has been prepared without regard to the disclosure standards for issuance prospectuses under art. 652a or art. 1156 of the Swiss Code of Obligations or the disclosure standards for listing prospectuses under art. 27 ff. of the SIX Listing Rules or the listing rules of any other stock exchange or regulated trading facility in Switzerland. Neither this document nor any other offering or marketing material relating to the shares or the offering may be publicly distributed or otherwise made publicly available in Switzerland.

Neither this document nor any other offering or marketing material relating to the offering, the Company, the shares have been or will be filed with or approved by any Swiss regulatory authority. In particular, this document will not be filed with, and the offer of shares will not be supervised by, the Swiss Financial Market Supervisory Authority FINMA (FINMA), and the offer of shares has not been and will not be authorized under the Swiss Federal Act on Collective Investment Schemes ("CISA"). The investor protection afforded to acquirers of interests in collective investment schemes under the CISA does not extend to acquirers of shares.

Dubai International Financial Centre

This prospectus supplement relates to an Exempt Offer in accordance with the Offered Securities Rules of the Dubai Financial Services Authority ("DFSA"). This prospectus supplement is intended for distribution only to persons of a type specified in the Offered Securities Rules of the DFSA. It must not be delivered to, or relied on by, any other person. The DFSA has no responsibility for reviewing or verifying any documents in connection with Exempt Offers. The DFSA has not approved this prospectus supplement nor taken steps to verify the information set forth herein and has no responsibility for the prospectus supplement. The shares to which this prospectus supplement relates may be illiquid and/or subject to restrictions on their resale. Prospective purchasers of the shares offered should conduct their own due diligence on the shares. If you do not understand the contents of this prospectus supplement you should consult an authorized financial advisor.

LEGAL MATTERS

Certain legal matters relating to the issuance of the shares of common stock will be passed upon for Onyx by Cooley LLP, Palo Alto, California. Davis Polk & Wardwell LLP, Menlo Park, California, is representing the underwriters in connection with this offering.

EXPERTS

Ernst & Young LLP, independent registered public accounting firm, has audited our consolidated financial statements included in our Annual Report on Form 10-K for the year ended December 31, 2011 and the effectiveness of our internal control over financial reporting as of December 31, 2011, as set forth in their report, which is incorporated by reference in this prospectus and elsewhere in the registration statement. Our financial statements are incorporated by reference in reliance on Ernst & Young LLP's report, given on their authority as experts in accounting and auditing.

Table of Contents

COMMON STOCK
PREFERRED STOCK
DEBT SECURITIES
WARRANTS

From time to time, we may offer to sell any combination of the securities described in this prospectus in amounts, at prices and on terms described in one or more supplements to this prospectus. We may also offer common stock or preferred stock upon conversion of debt securities, common stock upon conversion of preferred stock, or common stock, preferred stock or debt securities upon the exercise of warrants.

This prospectus describes some of the general terms that may apply to an offering of our common stock, preferred stock, debt securities or warrants. The specific terms and any other information relating to a specific offering will be set forth in a post-effective amendment to the registration statement of which this prospectus is a part or in a supplement to this prospectus or may be set forth in one or more documents incorporated by reference in this prospectus. We may also authorize one or more free writing prospectuses to be provided to you in connection with a specific offering.

We may offer and sell common stock, preferred stock, debt securities or warrants to or through one or more underwriters, dealers and agents, or directly to purchasers, on a continuous or delayed basis. The supplements to this prospectus and any authorized free writing prospectus will provide the specific terms of the plan of distribution.

Our common stock trades on the NASDAQ Global Select Market under the symbol "ONXX." On January 14, 2013, the last reported sale price of our common stock on the NASDAQ Global Select Market was $82.82 per share.

Investing in our securities 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 prospectus we have authorized for use in connection with a specific offering, and under similar headings in the documents that are incorporated by reference into this prospectus.

This prospectus may not be used to consummate a sale of 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 January 15, 2013

Table of Contents

TABLE OF CONTENTS

ABOUT THIS PROSPECTUS

This prospectus is part of a registration statement on Form S-3 that we filed with the Securities and Exchange Commission, or SEC, utilizing an "automatic shelf" registration process available to "well-known seasoned issuers," as defined in Rule 405 under the Securities Act of 1933, as amended, or the Securities Act. Under this shelf registration statement, we may offer and sell from time to time in one or more offerings the common stock, preferred stock, debt securities, warrants or any combination of these securities described in this prospectus. No limit exists on the aggregate number of shares of common stock, preferred stock or warrants, or the amount of debt securities we may sell pursuant to the registration statement. We may also offer common stock or preferred stock upon conversion of debt securities, common stock upon conversion of preferred stock, or common stock, preferred stock or debt securities upon the exercise of warrants.

Each time we offer securities 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.

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.

We have not authorized anyone to provide any information other than that contained or incorporated by reference in this prospectus or applicable prospectus supplement or free writing prospectus prepared by or on behalf of us or to which we have referred you. We take no responsibility for, and can provide no assurance as to the reliability of, any other information that others may give you. We are not making an offer to sell these securities, or soliciting an offer to buy these securities in any jurisdiction where the offer or sale is not permitted. You should not assume that the information contained in this prospectus, or in any prospectus supplement or authorized free writing prospectus, is accurate as of any date other than its date regardless of the time of delivery of the prospectus, prospectus supplement or authorized free writing prospectus or any sale of these securities.

We urge you to read carefully this prospectus, any applicable prospectus supplement and any authorized free writing prospectus, together with the information incorporated herein by reference as described under the heading "Where You Can Find More Information," before deciding whether to invest in any of the securities being offered.

This prospectus and the information incorporated herein by reference includes 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 or any applicable prospectus supplement or any authorized free writing prospectus are the property of their respective owners.

References in this prospectus to "Onyx," "we," "us" and "our" refer to Onyx Pharmaceuticals, Inc., a Delaware corporation, and its subsidiaries. Our website address is *http://www.onyx.com*. We do not incorporate the information on our website into this prospectus, and you should not consider it part of this prospectus.

RISK FACTORS

Investing in our securities involves risks. You should review carefully the risks and uncertainties described under the heading "Risk Factors" contained in any applicable prospectus supplement or authorized free writing prospectus and under similar headings in the other documents that are incorporated by reference into this prospectus before deciding whether to purchase any of the securities being registered pursuant to the registration statement of which this prospectus is a part. Each of the risk factors could adversely affect our business, operating results and financial condition, as well as adversely affect the value of an investment in our securities, and the occurrence of any of these risks might cause you to lose all or part of your investment. Moreover, the risks described are not the only ones that we face. Additional risks not presently known to us or that we currently believe are immaterial may also significantly impair our business operations.

SPECIAL NOTE REGARDING FORWARD-LOOKING STATEMENTS

This prospectus, the documents that we have filed with the SEC that are incorporated by reference in this prospectus and any authorized free writing prospectus contain forward-looking statements within the meaning of Section 27A of the Securities Act of 1933, as amended, or the Securities Act, and within the meaning of Section 21E of the Securities Exchange Act of 1934, as amended, or the Exchange Act, that are subject to the "safe harbor" created by those sections. These forward-looking statements can generally be identified as such because the context of the statement will include words such as "may," "will," "expect," "anticipate," "intend," "believe," "hope," "assume," "estimate," "plan," "future," "potential," "likely," "unlikely," "opportunity," "predict," "continue," "should," or the negative of these terms and similar expressions intended to identify forward-looking statements. Discussions containing these forward-looking statements may be found, among other places, in "Business" and in "Management's Discussion and Analysis of Financial Condition and Results of Operations" incorporated by reference from our most recent Annual Report on Form 10-K and from our Quarterly Reports on Form 10-Q for the quarterly periods ended subsequent to our filing of such Annual Report on Form 10-K, as well as any amendments thereto reflected in subsequent filings with the SEC. These forward-looking statements include but are not limited to statements about:

- our strategy;
- the progress, timing and results of our development programs, including clinical testing;
- sufficiency of our cash resources;
- revenues from existing and new collaborations;
- product development;
- our research and development and other expenses; and
- our operations and legal risks.

These forward-looking statements are based largely on our expectations and projections about future events and future trends affecting our business, and are subject to risks and uncertainties that could cause actual results to differ materially form those anticipated in the forward-looking statements. Before deciding to purchase our securities, you should carefully consider the risk factors described in

the "Risk Factors" section of this prospectus, in addition to the other information set forth in this prospectus, any applicable prospectus supplement, any authorized free writing prospectus and the documents incorporated by reference herein and therein.

In addition, past financial and/or operating performance is not necessarily a reliable indicator of future performance and you should not use our historical performance to anticipate results or future period trends. We can give no assurances that any of the events anticipated by the forward-looking

statements will occur or, if any of them do, what impact they will have on our results of operations and financial condition.

Except as required by law, we undertake no obligation to publicly revise our forward-looking statements to reflect events or circumstances that arise after the filing of this prospectus, any applicable prospectus supplement, any authorized free writing prospectus, or documents incorporated by reference herein and therein, that include forward-looking statements.

SELECTED FINANCIAL DATA

The following table sets forth our historical selected financial information. Effective January 1, 2012, we adopted the Financial Accounting Standards Board's ("FASB") Accounting Standards Update ("ASU") No. 2011-05, Comprehensive Income (Topic 220): Presentation of Comprehensive Income, as amended by ASU 2011-12, Comprehensive Income (Topic 220): Deferral of the Effective Date for Amendments to the Presentation of Reclassifications of Items Out of Accumulated Other Comprehensive Income in Accounting Standards Update No. 2011-05. These updates revise the manner in which entities present comprehensive income in their financial statements. The following selected financial information revises historical information to illustrate the new presentation required by this pronouncement for the periods presented.

STATEMENTS OF COMPREHENSIVE INCOME
(Unaudited, in thousands)

	Year Ended		
	December 31, 2009	December 31, 2010	December 31, 2011
Net income (loss)	$ 16,161	$ (84,847)	$ 76,110
Unrealized gain (loss) on available for sale securities	2,358	732	(781)
Unrealized gain (loss) on cash flow hedges	–	(61)	61
Comprehensive income (loss)	$ 18,519	$ (84,176)	$ 75,390

RATIO OF EARNINGS TO FIXED CHARGES

The table below sets forth our ratio of earnings to fixed charges for the periods indicated. "Earnings" consist of income (loss) from continuing operations before income taxes, extraordinary items, cumulative effect of accounting changes, equity in net losses of affiliates and fixed charges. "Fixed charges" consist of interest expense and the portion of operating lease expense that represents interest.

	Fiscal the Year Ended December 31,					Nine Months Ended
	2007	2008	2009	2010	2011	September 30, 2012
Ratio of earnings to fixed charges(1)	–	7.1	3.4	–	4.1	–

(1) For the fiscal years ended December 31, 2007 and 2010, and the nine months ended September 30, 2012, our earnings were insufficient to cover fixed charges by $34.2 million, $85.7 million, $240.6 million, respectively.

RATIO OF EARNINGS TO COMBINED FIXED CHARGES AND PREFERENCE DIVIDENDS

The table below sets forth our ratio of earnings to combined fixed charges and preference security dividends for the periods indicated. "Earnings" consist of income (loss) from continuing operations before income taxes, extraordinary items, cumulative effect of accounting changes, equity in net losses of affiliates and fixed charges. "Fixed charges" consist of interest expense and the portion of operating

lease expense that represents interest. "Preference dividends" consist of the amount of pre-tax earnings that is required to pay the dividends on outstanding preference securities.

	Fiscal the Year Ended December 31,					Nine Months Ended
	2007	2008	2009	2010	2011	September 30, 2012
Ratio of earnings to combined fixed charges and preference dividends(1)	–	7.1	3.4	–	4.1	–

(1) For the fiscal years ended December 31, 2007 and 2010, and the nine months ended September 30, 2012, our combined fixed charges and preference dividends exceeded earnings by $34.2 million, $85.7 million, $240.6 million, respectively.

USE OF PROCEEDS

Except as described in any prospectus supplement or in any related authorized free writing prospectus that we may authorize to be provided to you, we intend to use the net proceeds from the sale of securities issued pursuant to this registration statement to fund our clinical development program for carfilzomib and oprozomib, and for other research and development activities, both ongoing and planned, as well as sales and marketing activities to commercialize Kyprolis around the world, and for general corporate purposes, including working capital. We may also use a portion of our net proceeds from any such sale of securities to make potential milestone payments to the Proteolix shareholders; to pay a portion of or all of our $230 million convertible debt when due; to further build and diversify our pipeline by in-licensing products or product candidates or investing in or acquiring businesses or technologies that we believe are complementary to our own. We have no current commitments or agreements with respect to any such transactions. We have not determined the amounts we plan to spend on any of the areas listed above or the timing of these expenditures. As a result, our management will have broad discretion to allocate the net proceeds of these offerings. Pending the application of the net proceeds from these offerings, we expect to invest the proceeds in investment-grade, interest-bearing securities.

The 4.0% convertible senior notes due 2016, or the 2016 Notes, were issued in August 2009 and bear interest at a rate of 4.00% per year, payable semi-annually in arrears, on February 15 and August 15 of each year, commencing on February 15, 2010. The 2016 Notes mature on August 15, 2016, unless earlier converted, repurchased or redeemed.

DESCRIPTION OF CAPITAL STOCK

We may issue shares of our common stock from time to time, in one or more offerings. We will set forth in the applicable prospectus supplement a description of the terms of the offering of common stock, including the offering price, the net proceeds to us and other offering material relating to such offering.

We may issue shares of our preferred stock from time to time, in one or more offerings. We will set forth in the applicable prospectus supplement a description of the terms of the offering of preferred stock, including the offering price, rights, preferences, privileges, restrictions, the net proceeds to us and other offering material relating to such offering.

DESCRIPTION OF DEBT SECURITIES

We may issue shares of our debt securities from time to time, in one or more offerings. We will set forth in the applicable prospectus supplement a description of the terms of the offering of debt

securities, including maturity date, interest, the net proceeds to us and other offering material relating to such offering.

DESCRIPTION OF WARRANTS

We may issue warrants to purchase our common stock, preferred stock and/or debt securities, or any combination of the foregoing. Warrants may be issued independently or together with any other securities and may be attached to, or separate from, such securities. Each series of warrants will be issued under a separate warrant agreement to be entered into between us and a warrant agent. We will set forth in the applicable prospectus supplement a description of the terms of the offering of warrants, including the offering price, a description of the material provisions of the applicable warrant agreement, the net proceeds to us and other offering material relating to such offering.

LEGAL MATTERS

Unless otherwise indicated in the applicable prospectus supplement, the validity of the issuance of the securities offered by this prospectus and any supplement thereto will be passed upon for us by our counsel, Cooley LLP, Palo Alto, California. As of January 15, 2013, partners and associates of Cooley LLP participating in the preparation of this prospectus and the related Registration Statement on Form S-3 owned no shares of our common stock.

EXPERTS

Ernst & Young LLP, independent registered public accounting firm, has audited our consolidated financial statements included in our Annual Report on Form 10-K for the year ended December 31, 2011 and the effectiveness of our internal control over financial reporting as of December 31, 2011, as set forth in their report, which is incorporated by reference in this prospectus and elsewhere in the registration statement. Our financial statements are incorporated by reference in reliance on Ernst & Young LLP's report, given on their authority as experts in accounting and auditing.

WHERE YOU CAN FIND MORE INFORMATION

We file annual, quarterly and current reports, proxy statements and other information with the SEC. You may 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 more information about the operation of the public reference room. The SEC maintains an Internet site that contains reports, proxy and information statements, and other information regarding issuers that file electronically with the SEC, including Onyx Pharmaceuticals. The SEC's Internet site can be found at *http://www.sec.gov*.

INCORPORATION OF CERTAIN INFORMATION BY REFERENCE

The SEC allows us to incorporate by reference the information we file with it, which means that we can disclose important information to you by referring you to another document that we have filed separately with the SEC. You should read the information incorporated by reference because it is an important part of this prospectus. We incorporate by reference the following information or documents that we have filed with the SEC (Commission File No. 0-28298):

our Annual Report on Form 10-K, for the year ended December 31, 2011;

our Quarterly Reports on Form 10-Q for the quarters ended March 31, 2012, June 30, 2012 and September 30, 2012;

the information specifically incorporated by reference into our 2011 annual report on Form 10-K referred to above from our Definitive Proxy Statement on Schedule 14A, filed with the SEC on April 2, 2012;

our Current Reports on Form 8-K (other than information furnished rather than filed) filed February 8, 2012, February 16, 2012, May 22, 2012, July 20, 2012, and September 27, 2012; and

the description of our common stock set forth in our registration statement on Form 8-A, filed with the SEC on April 2, 1996, including any amendments or reports filed for the purposes of updating this description.

Any information in any of the foregoing documents will automatically be deemed to be modified or superseded to the extent that information in this prospectus or in a later filed document that is incorporated or deemed to be incorporated herein by reference modifies or replaces such information.

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) made with the SEC pursuant to Sections 13(a), 13(c), 14 or 15(d) of the Exchange Act, until we file a post-effective amendment which indicates the termination of the offering of the securities made by this prospectus. 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.

We will provide to each person, including any beneficial owner, to whom a prospectus is delivered, without charge upon written or oral request, a copy of any or all of the documents that are incorporated by reference into this prospectus but not delivered with the prospectus, including exhibits which are specifically incorporated by reference into such documents. You may request a copy of these filings at no cost by writing or telephoning us at the following address or telephone number:

Onyx Pharmaceuticals, Inc.
Attn: Investor Relations
249 E. Grand Avenue
South San Francisco, California 94080
Telephone number: (650) 266-0000

Shares

Onyx Pharmaceuticals, Inc.

Common Stock

PROSPECTUS SUPPLEMENT

BofA Merrill Lynch **Barclays**