ZIOPHARM ONCOLOGY INC
Form 424B5
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File No. 333-166444

PROSPECTUS SUPPLEMENT
(To Prospectus dated May 10, 2010)

9,600,000 Shares

Common Stock

This is an offering of 9,600,000 shares of the common stock of ZIOPHARM Oncology, Inc.

Our common stock trades on The NASDAQ Capital Market under the symbol ZIOP. The last reported trading price of our stock on February 2, 2011 was $6.20 per share.

Investing in our common stock involves risks. See Risk Factors beginning on page S-9 of this prospectus supplement and page 5 of the accompanying prospectus.

	Per Share	Total
Price to the public	$ 5.75	$ 55,200,000
Underwriting discounts and commissions	$ 0.325	$ 3,120,000
Proceeds to ZIOPHARM Oncology, Inc. (before expenses)	$ 5.425	$ 52,080,000

We have granted Barclays Capital a 30-day option to purchase up to an additional 1,440,000 shares of common stock on the same terms and conditions set forth above.

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

Barclays Capital expects to deliver the shares on or about February 8, 2011.

Barclays Capital

Prospectus Supplement dated February 3, 2011

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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 are 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.

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ABOUT THIS PROSPECTUS SUPPLEMENT

This document is in two parts. The first part is this prospectus supplement, which describes the terms of this offering of common stock and also adds to and updates information contained in the accompanying prospectus and the documents incorporated by reference into this prospectus supplement and the accompanying prospectus. The second part, the accompanying prospectus dated May 10, 2010, including the documents incorporated by reference therein, provides more general information. Generally, when we refer to this prospectus, we are referring to both parts of this document combined. To the extent there is a conflict between the information contained in this prospectus supplement, on the one hand, and the information contained in the accompanying prospectus or in any document incorporated by reference that was filed with the Securities and Exchange Commission, or SEC, before the date of this prospectus supplement, on the other hand, you should rely on the information in this prospectus supplement. If any statement in one of these documents is inconsistent with a statement in another document having a later date for example, a document incorporated by reference in the accompanying prospectus the statement in the document having the later date modifies or supersedes the earlier statement. 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 before making an investment decision.

All references in this prospectus supplement and the accompanying prospectus to ZIOPHARM Oncology, ZIOPHARM, the Company, we, us, our, or similar references refer to ZIOPHARM Oncology, Inc., except whe context otherwise requires or as otherwise indicated.

This prospectus supplement, the accompanying prospectus, and the information incorporated herein and therein by reference, include trademarks, service marks and trade names owned by us or other companies. All trademarks, service marks and trade names included or incorporated by reference into this prospectus supplement or the accompanying prospectus are the property of their respective owners.

You should rely only on the information contained or incorporated by reference in this prospectus supplement and the accompanying prospectus, along with the information contained in any free writing prospectus that we have authorized for use in connection with this offering. If the description of the offering varies between this prospectus supplement and the accompanying prospectus, you should rely on the information in this prospectus supplement. We have not authorized anyone to provide you with different or additional information. You should assume that the information appearing in this prospectus supplement, the accompanying prospectus, the documents incorporated by reference in this prospectus supplement and the accompanying prospectus, and any free writing prospectus that we have authorized for use in connection with this offering is accurate only as of the respective dates of those documents. Our business, financial condition, results of operations and prospects may have changed since those dates.

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PROSPECTUS SUPPLEMENT SUMMARY

This summary highlights certain information about us, this offering and selected information contained elsewhere in or incorporated by reference into this prospectus supplement. This summary is not complete and does not contain all of the information that you should consider before deciding whether to invest in our common stock. For a more complete understanding of our company and this offering, we encourage you to read and consider carefully the more detailed information in this prospectus supplement and the accompanying prospectus, including the information incorporated by reference in this prospectus supplement and the accompanying prospectus, and the information included in any free writing prospectus that we have authorized for use in connection with this offering, including the information referred to under the heading Risk Factors in this prospectus supplement beginning on page S-9.

Company Overview

ZIOPHARM Oncology, Inc. is a biopharmaceutical company that is seeking to develop and commercialize a diverse portfolio of in-licensed cancer drugs that can address unmet medical needs. Our principal focus has been on the licensing and development of proprietary small molecule drug candidates that are related to cancer therapeutics already on the market or in development and that can be administered by intravenous and/or oral dosing. On January 6, 2011, we entered into an Exclusive Channel Partner Agreement with Intrexon Corporation pursuant to which we will supplement our small molecule drug development efforts by pursuing the development and commercialization of novel DNA-based therapeutics in the field of cancer treatment using Intrexon s Rheoswitch® and UltraVector® synthetic biology technologies. *See* Recent Developments Exclusive Channel Partnership with Intrexon Corporation. This partnering arrangement contemplates our using Intrexon s advanced transgene engineering platform for the controlled and precise cellular production of anti-cancer effectors. Under the arrangement, we obtained rights to Intrexon s entire *in vivo* effector platform for use in the field of oncology, which includes two existing clinical-stage product candidates. The first lead product, INXN 3001/1001, is currently in a Phase Ib study and the second, INXN 2001/1001, is the basis of an Investigational New Drug (IND) application that we expect to submit during the first half of 2011. We plan to leverage Intrexon s synthetic biology platform for products to stimulate key pathways used by the body s immune system to inhibit the growth and metastasis of cancers, adding significantly to our small molecule drug development portfolio utilizing our global capabilities to translate science to the patient.

We believe that our strategy will result in expedited drug development programs with product candidates having a low cost of manufacturing that address changing reimbursement requirements around the world. We are currently in Phase I, II and/or III studies for four product candidates identified as palifosfamide (Zymafos™, ZIO-201), darinaparsin (Zinapar™, ZIO-101), indibulin (Zybulin™, ZIO-301), and INXN-3001/1001, with a particular emphasis on completing the recently initiated palifosfamide pivotal Phase III trial to support registration in combination with doxorubicin in the front-line setting of soft tissue sarcoma.

ZIO-201 or palifosfamide (Zymafos™) comprises the active metabolite of ifosfamide, a compound chemically related to cyclophosphamide. Patent applications covering proprietary forms of palifosfamide for pharmaceutical composition and method of use have been filed in the U.S. and internationally and in the U.S. we recently received a patent covering pharmaceutical composition. Like cyclophosphamide, ifosfamide and bendamustine, palifosfamide is a DNA alkylating agent, a form of cancer therapy to treat a wide range of solid tumors and hematological malignancies. We believe that cyclophosphamide is the most widely used alkylating agent in cancer therapy, with significant use in the treatment of breast cancer and non-Hodgkin s lymphoma. Bendamustine has been recently approved and successfully launched by Cephalon Oncology in the U.S. and Europe to treat certain hematological malignancies. Ifosfamide has been shown to be effective in the treatment of sarcoma and lymphoma, either by itself or in combination with other

anticancer agents. Ifosfamide is approved by the Food and Drug Administration (FDA) as a treatment for testicular cancer while ifosfamide-based treatment is a standard of care for sarcoma, although it is not approved for this indication by the FDA. Preclinical studies have shown that palifosfamide has activity against leukemia and solid tumors. These studies also indicate that palifosfamide may have a better safety profile than ifosfamide or cyclophosphamide because it does not appear to produce known toxic metabolites of ifosfamide, such as acrolein and chloroacetaldehyde. Acrolein, which is toxic to the kidneys and bladder, can mandate the administration of a protective agent

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called mesna, which is inconvenient and expensive. Chloroacetaldehyde is toxic to the central nervous system, causing fuzzy brain syndrome for which there is currently no protective measure. Similar toxicity concerns pertain to high-dose cyclophosphamide, which is widely used in bone marrow and blood cell transplantation. Palifosfamide has evidenced activity against ifosfamide- and/or cyclophosphamide-resistant cancer cell lines. Also in preclinical cancer models, palifosfamide was shown to be orally active and encouraging results have been obtained with palifosfamide in combination with doxorubicin, an agent approved to treat sarcoma.

Following completion of Phase I study, we completed Phase II testing of the intravenous form of palifosfamide as a single agent to treat advanced sarcoma. In both Phase I and Phase II testing, palifosfamide has been administered without the uroprotectant mesna, and the toxicities associated with acrolein and chloroacetaldehyde have not been observed. We reported clinical activity of palifosfamide when used alone in the Phase II study addressing advanced sarcoma. Following review of preclinical combination studies, clinical data, and discussion with sarcoma experts, we initiated a Phase I dose escalation study of palifosfamide in combination with doxorubicin primarily in patients with soft tissue sarcoma. We reported favorable results and safety profile from this study at ASCO s 2009 annual meeting. In light of reported favorable Phase II clinical activity data and with the combination being well tolerated in the Phase I trial, we initiated a Phase II randomized controlled trial in the second half of 2008 to compare doxorubicin plus palifosfamide to doxorubicin alone in patients with front- and second-line metastatic or unresectable soft tissue sarcoma. The study generated positive top line interim data in 2009. Upon successfully reaching a pre-specified efficacy milestone and following safety and efficacy data review by the Data Committee, sarcoma experts, and our Medical Advisory Board, we elected to suspend enrollment in the trial in October 2009. We subsequently presented further positive interim data from the trial at the 15th Annual Connective Tissue Oncology Society meeting held in November 2009 and again at the 2010 ASCO Annual Meeting where the presentation was also selected for Best of ASCO. In July 2010, we announced the initiation of a worldwide registration trial on a protocol design developed through a FDA End of Phase II meeting and the Special Protocol Assessment (SPA) process. Although the Company did engage in the SPA process, the Company, with guidance from the FDA, elected to initiate the trial without having obtained SPA agreement from the FDA. The Phase III trial is in front-line metastatic soft tissue sarcoma, entitled PICASSO 3, and is an international, randomized, double-blinded, placebo-controlled trial with a targeted enrollment of 424 patients. The study is designed to evaluate the safety and efficacy of palifosfamide administered with doxorubicin compared with doxorubicin administered with placebo, with no cross-over between the arms. Progression-free survival is the primary endpoint for accelerated approval, with overall survival as the primary endpoint for full approval. Orphan Drug Designation for palifosfamide has been obtained in both the United States and the European Union for the treatment of soft tissue sarcomas. As an orphan designated indication, the patient population available for participation in the PICASSO 3 trial is generally limited. To date, the company has experienced slower than anticipated enrollment in the PICASSO 3 trial and has recently taken steps to accelerate patient enrollment and address shortages of doxorubicin, a drug that is necessary for conduct of the trial.

We have also initiated a Phase I trial with palifosfamide in combination with etoposide and carboplatin to determine appropriate safety for initiating a subsequent randomized trial in front-line small-cell lung cancer (SCLC). An oral form of palifosfamide is expected to enter Phase I study in the first quarter of this year.

ZIO-101 or darinaparsin (Zinapar™) is an anti-mitochondrial (organic arsenic) compound covered by issued patents and pending patent applications in the U.S. and in foreign countries. A form of commercially available inorganic arsenic (arsenic trioxide [Trisenox ®] or ATO) has been approved in the United States, the European Union and Japan for the treatment of acute promyelocytic leukemia, a precancerous condition. In the United States, ATO is on the compendia listing for the therapy of multiple myeloma, and has been studied for the treatment of various other cancers. Nevertheless, ATO has been shown to be toxic to the heart, liver, and brain, which limits its use as an anti-cancer agent. ATO carries a black box warning for ECG abnormalities since arsenic trioxide has been shown to cause QT interval prolongation and complete atrioventricular block. QT prolongation can lead to a *torsade de*

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pointes-type ventricular arrhythmia, which can be fatal. Inorganic arsenic has also been shown to cause cancer of the skin and lung in humans. The toxicity of arsenic is generally correlated to its accumulation in organs and tissues. Our preclinical and clinical studies to date have demonstrated that darinaparsin is considerably less toxic than ATO, particularly with regard to cardiac toxicity. *In vitro* testing of darinaparsin using the National Cancer Institute s human cancer cell panel demonstrated activity against a series of tumor cell lines including lung, colon, brain, melanoma, ovarian, and kidney cancer. Moderate activity was shown against breast and prostate cancer tumor cell lines. In addition to solid tumors, *in vitro* testing in both the National Cancer Institute s cancer cell panel and *in vivo* testing in a leukemia animal model demonstrated substantial activity against hematological cancers (cancers of the blood and blood-forming tissues) such as leukemia, lymphoma, myelodysplastic syndromes, and multiple myeloma. Results indicate significant activity against the HuT 78 cutaneous T-cell lymphoma, the NK-G2MI natural killer-cell NHL, KARPAS-299 T-cell NHL, SU-DHL-8 B-cell NHL, SU-DHL-10 B-cell NHL and SU-DHL-16 B-cell NHL cell lines. Preclinical studies have also established anti-angiogenic properties of darinaparsin, provided support for the development of an oral form of the drug, and established synergy of darinaparsin in combination with other approved anti-cancer agents.

Phase I testing of the intravenous (IV) form of darinaparsin in solid tumors and hematological cancers was completed and we reported clinical activity and, importantly, a safety profile from these studies as predicted by preclinical results. We subsequently completed Phase II studies in advanced myeloma, primary liver cancer and in certain other hematological cancers. In addition, we have re-opened Phase I study with an oral form which is ongoing. At the May 2009 annual meeting of the American Society of Clinical Oncology, we reported favorable results from the trial with IV-administered darinaparsin in lymphoma, particularly peripheral T-cell lymphoma. We have initiated a Phase I study of darinaparsin with the combination treatment regimen called CHOP , which is standard of care for front-line peripheral T-cell lymphoma (PTCL), as a basis to address the front-line setting of PTCL. We presently plan to initiate a two-stage potentially pivotal trial likely in certain relapsed patients. We have obtained Orphan Drug Designation in the United States for the treatment of PTCL, and a positive recommendation from the Committee for Orphan Medicinal Products (COMP) within the European Medicines Agency (EMA) for designation as an orphan medicinal product for the same indication. Upon completion of the on-going Phase I oral study, we anticipate conducting a Phase II study in solid tumors that would build upon recently reported preclinical work in which darinaparsin had a significant cytotoxic and radiosensitizing effect against different cancer cells under both normal and hypoxic conditions.

ZIO-301 or indibulin (Zybulin™) is a novel, orally available small molecular-weight inhibitor of tubulin polymerization that we acquired from Baxter Healthcare in 2006 and is the subject of numerous patents worldwide, including the United States, the European Union and Japan. The microtubule component, tubulin, is one of the more well established drug targets in cancer. Microtubule inhibitors interfere with the dynamics of tubulin polymerization, resulting in inhibition of chromosome segregation during mitosis and consequently inhibition of cell division. A number of marketed IV anticancer drugs target tubulin, such as the taxane family members, paclitaxel (Taxol®), docetaxel (Taxotere®), the Vinca alkaloid family members, vincristine and vinorelbine, and new classes of tubulin inhibitors including the epothilones. This class of agents is typically the mainstay of therapy in a wide variety of indications. In spite of their effectiveness, the use of these drugs is associated with significant toxicities, notably peripheral neurotoxicity.

Preclinical studies with indibulin demonstrate significant and broad antitumor activity, including activity against taxane-refractory cell lines. The cytotoxic activity of indibulin was demonstrated in several rodent and human tumor cell lines derived from prostate, brain, breast, pancreas, lung, ovary, and cervical tumor tissues and in rodent tumor and human tumor xenograft models. In addition, indibulin was effective against multidrug resistant tumor cell lines (breast, lung, and leukemia) both *in vitro* and *in vivo*. Indibulin is potentially safer than other tubulin inhibitors. No neurotoxicity has been observed at therapeutic doses in rodents and in the Phase I trials. Indibulin has also demonstrated synergy with approved anti-cancer agents in preclinical studies. The availability of an oral formulation of indibulin creates significant commercial opportunity because no oral capsule formulations of the taxane family are

currently on the market in the United States.

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Indibulin, as a single agent, has completed a Phase I study in patients with advanced solid tumors. We have reported clinical activity at well-tolerated doses using a continuous dosing scheme without the development of clinically relevant peripheral neuropathy. Following encouraging results obtained with indibulin in combination with erlotinib, and 5-FU in preclinical models, two Phase I combination studies were initiated with Tarceva™ and Xeloda™, respectively. Favorable activity and safety profile of oral indibulin with oral Xeloda™ were reported at ASCO s annual meeting in May 2009. Preclinical work with our consultant, Dr. Larry Norton, to explore dose scheduling for the clinical setting have been completed, with results supporting the recently initiated Phase I safety trial necessary for a Phase II breast cancer trial and using the mathematical dosing schedule established preclinically. We have recently modified the dosage form to be able to administer a smaller number of capsules and expect to substitute the new dosage form into our ongoing Phase I trial in the first quarter of this year.

INXN 3001/1001 (or DC-RTS-IL-12) and INXN 2001/1001 (or Ad-RTS-IL-12) are the two lead clinical-stage projects currently in development under our partnering arrangement with Intrexon Corporation.
INXN 3001/1001 is in a Phase Ib trial in the U.S. and employs intratumoral injection of modified dendritic cells from each patient (INXN-3001) and oral dosing of an activator ligand (INXN-1001) to turn on *in vivo* expression of interleukin-12 (IL-12). INXN-3001/1001 uses the RheoSwitch Therapeutic System (RTS™) to control the timing and level of transgene expression for gene and cell therapy. RTS™ functions as a gene switch for the regulated expression of human IL-12 in the patients dendritic cells, which are transduced with a replication-deficient adenoviral vector carrying the IL-12 gene under the control of the RTS™ and in this study injected intratumorally for the treatment of patients with stage III or IV melanoma. The binding of the small molecule activator to the fusion proteins of RTS™ is intended to regulate the timing and level of IL-12 expression. In the absence of the activator ligand, the level of Il-12 is below detectable levels.

The activator ligand has been the subject of a number of preclinical, safety and pharmacology studies under FDA and ICH guidelines. Preclinical studies in the B16 mouse melanoma model consistently induced regression of established melanoma lesions, both in those directly injected and those elsewhere in the body. Preclinical studies have shown DC-RTS-IL-12, in combination with INXN-1001, to have strong activity against a broad array of cancers, including brain, colon, renal, and pancreatic cancers and melanoma.

A Phase Ia clinical study of the activator ligand was conducted in 65 healthy volunteers, with the two most common side effects being dysgeusia (impairment of taste) and throat irritation. In the subsequent Phase Ib trial, which is now ongoing in patients with advanced melanoma, one patient reported a severe adverse event that constitutes a dose limiting toxicity (DLT). According to the protocol, additional patients are being evaluated to determine if the dose escalation will continue or the maximum tolerated dose has been reached. Among the first four patients treated, one patient demonstrated an overall partial response and a second demonstrated a response in some lesions. The Phase Ib trial has been amended to study efficacy and immunological and biological effects in addition to safety with cohort-based dose escalation of the activator ligand during repeated treatment cycles.

INXN 2001/1001 is expected to enter the clinic in the first half of this year, also targeting treatment of patients with late-stage malignant melanoma. We intend to evaluate both product candidates with the intent either to further develop both candidates or to select one of the two candidates for further study. INXN 2001/1001 is identical to INXN 3001/1001 except that the autologous dendritic cell component (INXN-3001) is omitted.

Recent Developments

Exclusive Channel Partnership with Intrexon Corporation

On January 6, 2011, we entered into an Exclusive Channel Partner Agreement (the Channel Agreement) with Intrexon Corporation (Intrexon) that governs a channel partnering arrangement in which we will use Intrexon s technology directed towards *in vivo* expression of effectors in connection with the development of clinical-stage product candidates and generally to research, develop and commercialize products, in each case in which DNA is administered to humans for expression of anti-cancer effectors for the purpose of treatment or prophylaxis of cancer.

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Intrexon Corporation Private Placement and Equity Commitment

In connection with the Channel Agreement, we entered into a Stock Purchase Agreement and Registration Rights Agreement with Intrexon. On January 12, 2011, and pursuant to that Stock Purchase Agreement, Intrexon purchased 2,426,235 shares of our common stock in a private placement for a total purchase price of $11,645,928, or $4.80 per share. We simultaneously issued to Intrexon for no additional consideration an additional 3,636,926 shares of our common stock. Under the terms of the Stock Purchase Agreement, we have agreed to issue to Intrexon an additional 3,636,926 shares of our common stock for no additional consideration under certain conditions upon dosing of the first patient in a ZIOPHARM-conducted U.S. Phase II clinical trial of a product candidate created, produced or developed by us using Intrexon technology. Pursuant to the Registration Rights Agreement, we have agreed to file a registration statement with the SEC registering the resale of the shares that we have issued or may issue to Intrexon under the Stock Purchase Agreement.

Also under the Stock Purchase Agreement, Intrexon has agreed that, subject to certain conditions and restrictions and limitations, it will purchase our securities in conjunction with qualified securities offerings that we conduct while the Channel Agreement remains in effect. In conjunction with a particular qualified offering, Intrexon has committed to purchase up to 19.99% of the securities offering and sold therein (exclusive of Intrexon s purchase) if requested to do so by us. However, Intrexon will not be obligated to purchase securities in a qualified securities offering unless we are then in substantial compliance with our obligations under the Channel Agreement and, with respect to a qualified securities offering that is completed following January 6, 2012, we confirm our intent that 40% of the offering s net proceeds shall have been spent, or in the next year will be spent, by us under the Channel Agreement. In the case of a qualified securities offering that is completed after January 6, 2012, Intrexon s purchase commitment will be further limited to an amount equal to one-half of the proceeds spent or to be spent by us under the Channel Agreement. Intrexon s aggregate purchase commitment for all future qualified offerings is capped at $50.0 million. The Company and Intrexon subsequently amended the Stock Purchase Agreement to clarify that gross proceeds from the sale of Company securities to Intrexon in a qualified offering will apply against Intrexon s $50.0 million purchase commitment regardless of whether Intrexon participates voluntarily or at the request of the Company.

Summary Development Plans

The successful development of our product candidates is highly uncertain. Product development costs and timelines can vary significantly for each product candidate, are difficult to accurately predict, and will require us to obtain additional funding, either alone or in connection with partnering arrangements. Various statutes and regulations also govern or influence the manufacturing, safety, labeling, storage, record keeping and marketing of each product. The lengthy process of seeking approval and the subsequent compliance with applicable statutes and regulations require the expenditure of substantial resources. Any failure by us to obtain, or any delay in obtaining, regulatory approvals could materially, adversely affect our business. To date, we have not received approval for the sale of any product candidates in any market and, therefore, have not generated any revenues from our product candidates.

After giving effect to the sale and issuance of 9,600,000 shares of common stock in this offering, and given our current plans to use internal financial resources to develop palifosfamide and pursue the clinical work discussed above, but with the intention of partnering or otherwise raising additional resources to support further development activities for all of our product candidates, we expect to incur the following expenses during the next twelve months: approximately $57.5 million on research and development expenses and approximately $10.4 million on general corporate and administrative expenses. With our current cash position, we believe that we currently have sufficient capital that will support our current operations until late 2012. Our forecast of the period of time through which our financial resources will be adequate to support our operations, the costs to complete development of products and the

cost to commercialize our future products are forward-looking statements and involve risks and uncertainties, and actual results could vary materially and negatively as a result of a number of factors, including the factors discussed in the Risk Factors section of this prospectus. We have based these estimates on assumptions that may prove to be wrong, and we could exhaust our available capital resources sooner than we currently expect. Specifically, we commenced a

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registration trial for IV palifosfamide early in the third quarter of 2010. We have estimated the sufficiency of our cash resources based in part on this trial design and our timing expectations for enrollment in the study.

In addition, we assumed responsibility for two product candidates under our exclusive channel partnership with Intrexon Corporation in early January 2011. We expect that the costs associated with these additional product candidates will increase the level of our overall research and development expenses significantly going forward. Although all human clinical trials are expensive and difficult to design and implement, we believe that costs associated with clinical trials for synthetic biology products are greater than the corresponding costs associated with clinical trials for small molecule candidates. In addition to increased research and development costs, we have added headcount in part to support our exclusive channel partnership endeavors and are opening a small office in the greater Washington D.C. area, which will add to our general and administrative expenses going forward. Although our forecasts for expenses and the sufficiency of our capital resources takes into account our plans to develop the Intrexon products, we have only recently assumed development responsibility for these products and the actual costs associated therewith may be significantly in excess of forecast amounts. In addition to the amount and timing of expenses related to the clinical trials, our actual cash requirements may vary materially from our current expectations for a number of other factors that may include, but are not limited to, changes in the focus and direction of our development programs, competitive and technical advances, costs associated with the development of our product candidates, our ability to secure partnering arrangements, and costs of filing, prosecuting, defending and enforcing our intellectual property rights. If we exhaust our capital reserves more quickly than anticipated, regardless of the reason, and we are unable to obtain additional financing on terms acceptable to us or at all, we will be unable to proceed with development of some or all of our product candidates on expected timelines and will be forced to prioritize among them.

Financial Update

The following table sets forth the Company s forecast of selected financial data at December 31, 2010 and for the three month and twelve month periods then ended, as well as selected financial data of the Company at December 31, 2009 and for the three month and twelve month periods then ended. The selected financial data at December 31, 2009 and for the twelve month period then ended are derived from our audited financial statements included in our annual report on Form 10-K for the fiscal year ended December 31, 2009, which is filed with the SEC and incorporated by reference into this prospectus supplement and the prospectus to which it relates. You should read such selected financial data in conjunction with the corresponding audited financial statements and the related notes and with Management s Discussion and Analysis of Financial Condition and Results of Operations included in such annual report on Form 10-K and generally in the periodic reports that we file with the SEC. Our forecast of selected financial data at December 31, 2010 and for the three month and twelve month periods then ended is preliminary in nature, has not been audited and is subject to change upon completion of our ongoing audit. Therefore, our actual financial condition and results of operations at December 31, 2010 and for the three month and twelve month periods then ended may differ materially from the forecasts reflected above and we assume no obligation to update the disclosures in this prospectus based upon our actual financial results. Moreover, this data does not reflect the proceeds from the sale of shares of our common stock to Intrexon Corporation on January 12, 2011 in a private placement transaction for a purchase price of approximately $11.6 million. Additional information and disclosures would be required for a more complete understanding of our financial position as of December 31, 2010 and our results of operations for the periods then ended.

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Balance Sheet Data
(in thousands)

	December 31, 2010 (unaudited)	December 31, 2009
Cash and cash equivalents	$ 60,392	$ 48,839
Working capital	$ 57,208	$ 46,098
Total assets	$ 61,543	$ 49,736
Current liabilities	$ 3,631	$ 3,095
Warrant liabilities	$ 27,311	$ 18,471
Total liabilities	$ 30,986	$ 21,632
Total stockholders' equity	$ 30,557	$ 28,104

Condensed Statements of Operations
(in thousands except share and per share data)

	For the Three Months Ended December 31,		For the Year Ended December 31,	
	2010 (unaudited)	2009 (unaudited)	2010 (unaudited)	2009
Research contract revenue	$	$	$	$
Operating expenses:				
Research and development, including costs of research contracts	3,054	1,216	12,927	4,556
General and administrative	3,302	2,813	11,615	7,567
Total operating expenses	6,356	4,029	24,542	12,123
Loss from operations	(6,356)	(4,029)	(24,542)	(12,123)
Other income, net	735	12	765	13
Change in fair value of warrants	(6,226)	4,981	(8,889)	4,461
Net loss	$(11,847)	$964	$(32,666)	$(7,649)
Basic and diluted net loss per share	$(0.25)	$0.03	$(0.71)	$(0.33)
Weighted average common shares outstanding used to compute basic and diluted net loss per share	48,039,345	28,002,429	46,003,679	23,108,039

Corporate Information

We were originally incorporated in Colorado in September 1998 (under the name Net Escapes, Inc.) and later changed our name to EasyWeb, Inc. in February 1999. We were re-incorporated in Delaware on May 16, 2005 under the same name. On September 13, 2005, we completed a reverse acquisition of privately held ZIOPHARM, Inc., a Delaware corporation. To effect this transaction, we caused ZIO Acquisition Corp., our wholly-owned subsidiary, to merge with and into ZIOPHARM, Inc., with ZIOPHARM, Inc. surviving as our wholly owned subsidiary. In accordance with the terms of the merger, the outstanding common stock of ZIOPHARM, Inc. automatically converted into the right to receive an aggregate of approximately 97.3% of our outstanding common stock (after giving effect to the transaction). Following the merger, we caused ZIOPHARM, Inc. to merge with and into us and we changed our name to

ZIOPHARM Oncology, Inc. Although EasyWeb, Inc. was the legal acquirer in the transaction, we accounted for the transaction as a reverse acquisition under generally accepted accounting principles. As a result, ZIOPHARM, Inc. became the registrant with the SEC and the historical financial statements of ZIOPHARM, Inc. became our historical financial statements.

Our executive offices are located at 1180 Avenue of the Americas, 19th Floor, New York, NY 10036, and our telephone number is (646) 214-0700. Our internet site is www.ziopharm.com. None of the information on our internet site is part of this prospectus. As of January 27, 2011, we had 32 full time and one part time employees.

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THE OFFERING

Common stock we are offering **9,600,000 shares**

Common stock covered by the underwriter s option to purchase additional shares **1,440,000 shares**

Common stock outstanding immediately following this offering (excluding any shares subject to the underwriter s option to purchase additional shares) **64,212,866 shares**

Risk Factors

Investing in our common stock involves a high degree of risk. See Risk Factors beginning on page S-9.

NASDAQ Capital Market Symbol **ZIOP**

Outstanding Shares

The number of shares of common stock to be outstanding immediately after this offering, as shown above, assumes that all of the shares offered hereby are sold and is based on 54,612,866 shares of common stock outstanding as of January 27, 2011.

The number of shares does not include 1,440,000 shares subject to the underwriter s option to purchase additional shares and also excludes, as of January 27, 2011:

4,736,852 shares of our common stock issuable upon the exercise of stock options outstanding as of January 27, 2011, having a weighted average exercise price of $3.46 per share;
1,808,401 shares of our common stock available as of January 27, 2011 for future issuance pursuant to our 2003 Stock Option Plan;
15,912,142 shares of our common stock issuable upon the exercise of outstanding warrants as of January 27, 2011 with a weighted-average exercise price of $4.11 per share; and
3,636,926 shares of our common stock that will be issued contingent upon satisfaction of a development milestone under our Stock Purchase Agreement dated January 6, 2011 with Intrexon Corporation. *See Recent Developments Intrexon Corporation Private Placement and Equity Commitment.*

Except as otherwise indicated, all information in this prospectus supplement assumes no exercise by the underwriter of its over allotment option.

Intrexon Corporation Purchase

Intrexon Corporation, a corporation affiliated with Randal J. Kirk, who serves as a director of the Company, agreed to purchase 1,910,000 shares of common stock in this offering.

Use of Proceeds

We intend to use the net proceeds from this public offering for the overall development of our drug candidates, including to further expand the clinical trial programs, and for general corporate and working capital purposes. See Use of Proceeds on page S-24 of this prospectus supplement.

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RISK FACTORS

An investment in our common stock involves a high degree of risk. Before deciding whether to invest in our common stock, you should consider carefully the risks described below and discussed under the section captioned Risk Factors contained in our Quarterly Report on Form 10-Q for the period ended September 30, 2010, which is incorporated by reference in this prospectus supplement and the accompanying prospectus in its entirety, together with other information in this prospectus supplement, the accompanying prospectus, the information and documents incorporated by reference, and in any free writing prospectus that we have authorized for use in connection with this offering. If any of these risks actually occurs, our business, financial condition, results of operations or cash flow could be harmed. This could cause the trading price of our common stock to decline, resulting in a loss of all or part of your investment. The risks described below and in the documents referenced above are not the only ones that we face. Additional risks not presently known to us or that we currently deem immaterial may also affect our business.

Risks Related to this Offering

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

Our management will have broad discretion in the application of the net proceeds from this offering and could spend the proceeds in ways that do not improve our results of operations or enhance the value of our common stock. Our failure to apply these funds effectively could have a material adverse effect on our business, delay the development of our product candidates and cause the price of our common stock to decline.

You will experience immediate and substantial dilution in the net tangible book value per share of the common stock you purchase.

Since the price per share of our common stock being offered is substantially higher than the net tangible book value per share of our common stock, you will suffer substantial dilution in the net tangible book value of the common stock you purchase in this offering. Based on the public offering price of $5.75 per share in this offering, and after deducting underwriting discounts and commissions and estimated offering expenses payable by us and taking into account the sale and issuance of 6,063,161 shares of common stock to Intrexon Corporation on January 12, 2011, and based on a net tangible book value of our common stock of $0.87 per share as of September 30, 2010, if you purchase shares of common stock in this offering, you will suffer immediate and substantial dilution of $4.11 per share in the net tangible book value of common stock. See the section entitled Dilution below for a more detailed discussion of the dilution you will incur if you purchase common stock in this offering.

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

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

We are required to register the resale of a substantial number of shares of our common stock that have been and will be issued to Intrexon Corporation and the sale of those shares could adversely affect our stock price.

In connection with our issuance and sale of 6,063,131 shares of common stock to Intrexon Corporation on January 12, 2011 in a private sale, we agreed to file a registration statement on Form S-3 registering the resale of such shares on or before May 11, 2011 and to use our reasonable best efforts to cause the Registration Statement to become effective. If the selling stockholder(s) named in such resale registration statement sell, or indicate an intention to sell, all or a substantial portion of such shares after the registration is declared effective by the SEC, the trading price of our common stock could be adversely affected.

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Risks Related to our Exclusive Channel Partnership with Intrexon Corporation

The technology on which our channel partnering arrangement with Intrexon Corporation is based is early stage biotechnology in the field of human oncologic therapeutics.

Our exclusive channel partnership with Intrexon Corporation contemplates our using Intrexon s advanced transgene engineering platform for the controlled and precise cellular production of anti-cancer effectors. The in vivo effector platform in which we have acquired rights represents early-stage technology in the field of human oncologic therapeutics, with INXN 3001/1001 currently in a Phase Ib study and INXN 2001/1001 the basis of an IND application that we expect to submit during the first half of 2011. Although we plan to leverage Intrexon s synthetic biology platform for additional products targeting key pathways used by cancers to grow and metastasize, we may not be successful in developing and commercializing these products for a variety of reasons. The risk factors set forth in this prospectus that apply to our small molecule drug candidates, which are various stages of development, also apply to product candidates that we seek to develop under our exclusive channel partnership with Intrexon Corporation.

We will incur additional expenses in connection with the exclusive Intrexon channel partnership.

The *in vivo* effector platform in which we have acquired rights from Intrexon Corporation includes two existing product candidates, with INXN 3001/1001 currently in a Phase Ib study and INXN 2001/1001 the basis of an IND application that we expect to submit during the first half of 2011. Upon entry into the exclusive channel partnership with Intrexon we assumed responsibility for the clinical development of these product candidates, which we expect will increase the level of our overall research and development expenses significantly going forward. Although all human clinical trials are expensive and difficult to design and implement, we believe that costs associated with clinical trials for synthetic biology products are greater than the corresponding costs associated with clinical trials for small molecule candidates. In addition to increased research and development costs, we have added headcount in part to support our exclusive channel partnership endeavors and are opening a small office in the greater Washington D.C. area, which will add to our general and administrative expenses going forward.

Although our forecasts for expenses and the sufficiency of our capital resources set forth elsewhere in this prospectus supplement takes into account our plans to develop the Intrexon products, we have only recently assumed development responsibility for these products and the actual costs associated therewith may be significantly in excess of forecast amounts. In addition to the amount and timing of expenses related to the clinical trials, our actual cash requirements may vary materially from our current expectations for a number of other factors that may include, but are not limited to, changes in the focus and direction of our development programs, competitive and technical advances, costs associated with the development of our product candidates and costs of filing, prosecuting, defending and enforcing our intellectual property rights. If we exhaust our capital reserves more quickly than anticipated, regardless of the reason, and we are unable to obtain additional financing on terms acceptable to us or at all, we will be unable to proceed with development of some or all of our product candidates on expected timelines and will be forced to prioritize among them.

We are required to register the resale of a substantial number ofshares of our common stock that have been and wi

Risks Related to our Business

We will require additional financial resources in order to continue on-going development of our product candidates; if we are unable to obtain these additional resources, we may be forced to delay or discontinue clinical testing of our product candidates.

We have never generated revenue and have incurred significant net losses in each year since our inception. For the nine months ended September 30, 2010, we had a net loss of $20.8 million and we had incurred approximately $112.0 million of cumulative net losses since our inception in 2003. We expect to continue to incur significant operating expenditures. Further development of our product candidates, including product candidates that we develop under our channel partnering arrangement with Intrexon Corporation, will likely require substantial increases in our expenses as we:

- Continue to undertake clinical trials for product candidates;
- Continue with the formulation, manufacturing and scale-up of our product candidates;
- Seek regulatory approvals for product candidates;

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Implement additional internal systems and infrastructure; and
Hire additional personnel.

We continue to seek additional financial resources to fund the further development of our product candidate portfolio. If we are unable to obtain sufficient additional capital, one or more of these programs could be placed on hold. Because we are currently devoting a significant portion of our resources to the development of palifosfamide, further progress with the development and our other candidates may be significantly delayed and may depend on the success of our ongoing clinical trial involving palifosfamide.

Other than the Intrexon equity commitment (*See Recent Developments Intrexon Corporation Private Placement and Equity Commitment.*), we have no current committed sources of additional capital. We do not know whether additional financing will be available on terms favorable or acceptable to us when needed, if at all. Our business is highly cash-intensive and our ability to continue operations after our current cash resources are exhausted depends on our ability to obtain additional financing and achieve profitable operations, as to which no assurances can be given. If adequate additional funds are not available when required, or if we are unsuccessful in entering into partnership agreements for the further development of our small molecule products, we will be required to delay, reduce or eliminate planned preclinical and clinical trials and may be forced to terminate the approval process for our product candidates from the FDA or other regulatory authorities. In addition, we could be forced to discontinue product development, forego attractive business opportunities or pursue merger or divestiture strategies. In the event we are unable to obtain additional financing, we may be forced to cease operations altogether.

We need to raise additional capital to fund our operations. The manner in which we raise any additional funds may affect the value of your investment in our common stock.

As of September 30, 2010, we had incurred approximately $112.0 million of cumulative net losses and had approximately $66.5 million of cash and cash equivalents. After giving effect to the sale of 9,600,000 shares of our common stock in this offering and given our current plans for development of our product candidates, we anticipate that our cash resources will be sufficient to fund our operations until late 2012. However, changes may occur that would consume our existing capital prior to that time, including the scope and progress of our research and development efforts and changes in governmental regulation. Actual costs may ultimately vary from our current expectations, which could materially impact our use of capital and our forecast of the period of time through which our financial resources will be adequate to support our operations. Specifically, we commenced the PICASSO 3 pivotal trial for IV palifosfamide early in the third quarter of 2010. We have estimated the sufficiency of our cash resources based in part on this trial design and our timing expectations for enrollment in the study. In addition, our forecast anticipates the initiation of a two-stage potentially pivotal trial for the study of darinaparsin in combination with CHOP for the treatment of PTCL, likely in certain relapsed patients. We also recently assumed responsibility for two product candidates under our exclusive channel partnership with Intrexon Corporation and we expect that the costs associated with these additional product candidates will increase the level of our overall research and development expenses significantly going forward. Although our forecasts for expenses and the sufficiency of our capital resources takes into account our plans to develop the Intrexon products, we have only recently assumed development responsibility for these products and the actual costs associated therewith may be significantly in excess of forecast amounts. In addition to these factors our actual cash requirements may vary materially from our current expectations for a number of other factors that may include, but are not limited to, changes in the focus and direction of our development programs, competitive and technical advances, costs associated with the development of our product candidates, our ability to secure partnering arrangements, and costs of filing, prosecuting, defending and enforcing our intellectual property rights. *See Prospectus Supplement Summary Summary Development Plans.* If we

exhaust our capital reserves more quickly than anticipated, regardless of the reason, and we are unable to obtain additional financing on terms acceptable to us or at all, we will be unable to proceed with development of some or all of our product candidates on expected timelines and will be forced to prioritize among them.

Recently, capital markets have experienced a period of unprecedented instability that may severely hinder our ability to raise capital within the time periods needed or on terms we consider acceptable, if at all. Moreover, if we fail to advance one or more of our current product candidates to later-stage clinical trials,

We need to raise additional capital to fund our operations. Themanner in which we raise any additional funds may a

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successfully commercialize one or more of our product candidates, or acquire new product candidates for development, we may have difficulty attracting investors that might otherwise be a source of additional financing.

In the current economic environment, our need for additional capital and limited capital resources may force us to accept financing terms that could be significantly more dilutive than if we were raising capital when the capital markets were more stable. To the extent that we raise additional capital by issuing equity securities, our stockholders may experience dilution. In addition, we may grant future investors rights superior to those of our existing stockholders. If we raise additional funds through collaborations and licensing arrangements, it may be necessary to relinquish some rights to our technologies, product candidates or products, or grant licenses on terms that are not favorable to us. If we raise additional funds by incurring debt, we could incur significant interest expense and become subject to covenants in the related transaction documentation that could affect the manner in which we conduct our business.

Clinical trials are very expensive, time-consuming, and difficult to design and implement.

Human clinical trials are very expensive and difficult to design and implement, in part because they are subject to rigorous regulatory requirements. The clinical trial process itself is also time-consuming. We estimate that clinical trials of our product candidates will take at least several years to complete. Furthermore, failure can occur at any stage of the trials, and we could encounter problems that cause us to abandon or repeat clinical trials. The commencement and completion of clinical trials may be delayed by several factors, including:

Unforeseen safety issues;
Determination of dosing issues;
Lack of effectiveness during clinical trials;
Slower than expected rates of patient recruitment and enrollment;
Inability to monitor patients adequately during or after treatment;
Inability or unwillingness of medical investigators to follow our clinical protocols; and
Regulatory determinations to temporarily or permanently cease enrollment for other reasons not related to patient safety.

We commenced the PICASSO 3 pivotal trial for IV palifosfamide early in the third quarter of 2010. The trial is in front-line metastatic soft tissue sarcoma, entitled PICASSO 3, and is an international, randomized, double-blinded, placebo-controlled trial with a targeted enrollment of 424 patients. To date, the Company has experienced slower than anticipated enrollment in the trial due in part to the timing of regulatory approvals for opening trials sites and unanticipated contractual delays attributable to international healthcare budgetary constraints. The Company has taken steps to accelerate patient enrollment in order to meet its previous forecasted timeline for full enrollment by the end of 2011, including utilizing significantly more trial sites in the United States and elsewhere. However, the Company cannot assure that it will be able to enroll sufficient numbers of patients in the PICASSO trial to meet its previous forecast for full enrollment. As an orphan designated indication, the patient population available for participation in the PICASSO 3 trial is generally limited. Also affecting the enrollment and pace of the study is a recent limited supply of doxorubicin necessary for the trial. If the Company cannot accelerate enrollment in the PICASSO 3 study to meet its forecasted timeline, if limited supply of doxorubicin prevents treatment of patients in the trial, or the trial is delayed for other reasons, the delay will postpone our receipt of results from the trial and, consequently, our ability to submit a corresponding NDA with FDA for regulatory approval in accordance with our plans. *See also Risk Factors Our product candidates are in various stages of clinical trials, which are very expensive and time-consuming. We cannot be certain when we will be able to file an NDA or BLA with the FDA and any failure or delay in completing clinical trials for our product candidates could harm our business.*

We have received Orphan Drug status for palifosfamide in both the United States and Europe, for darinaparsin in the United States and pending final notification in Europe and we are hopeful that we may be able to obtain Fast Track and/or additional Orphan Drug status from the FDA, Europe and certain other

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countries for our product candidates. Fast Track allows the FDA to facilitate development and expedite review of drugs that treat serious and life-threatening conditions so that an approved product can reach the market expeditiously. Fast Track status does not apply to a product alone, but applies to a combination of a product and the specific indications for which it is being studied. Therefore, it is a drug s development program for a specific indication that receives Fast Track designation. Orphan Drug status promotes the development of products that demonstrate the promise for the diagnosis and treatment of one disease or condition affecting fewer than 200,000 patients in the U.S. and affords certain financial and market protection benefits to successful applicants. There is no guarantee that any of our other product candidates will be granted Orphan Drug status or will be granted Fast Track status by the FDA or that, even if such product candidate is granted such status, the product candidate s clinical development and regulatory approval process will not be delayed or will be successful.

In addition, we or the FDA may suspend our clinical trials at any time if it appears that we are exposing participants to unacceptable health risks or if the FDA finds deficiencies in our IND submission or in the conduct of these trials. For example, the Phase 1a study of INXN 3001/1001 was previously placed on clinical hold for safety concerns relating to intra-patient dose escalation. Therefore, we cannot predict with any certainty the schedule for future clinical trials.

We may not be able to commercialize any products, generate significant revenues, or attain profitability.

To date, none of our product candidates have been approved for commercial sale in any country. The process to develop, obtain regulatory approval for, and commercialize potential product candidates is long, complex, and costly. Unless and until we receive approval from the FDA and/or other regulatory authorities for our product candidates, we cannot sell our products and will not have product revenues. Even if we obtain regulatory approval for one or more of our product candidates, if we are unable to successfully commercialize our products, we may not be able to generate sufficient revenues to achieve or maintain profitability, or to continue our business without raising significant additional capital, which may not be available. Our failure to achieve or maintain profitability could negatively impact the trading price of our common stock.

We have a limited operating history upon which to base an investment decision.

We are a development-stage company that was incorporated in September 2003. To date, we have not demonstrated an ability to perform the functions necessary for the successful commercialization of any product candidates. The successful commercialization of any product candidates will require us to perform a variety of functions, including:

Continuing to undertake preclinical development and clinical trials;
Participating in regulatory approval processes;
Formulating and manufacturing products; and
Conducting sales and marketing activities.

Our operations have been limited to organizing and staffing our Company, acquiring, developing, and securing our proprietary product candidates, and undertaking preclinical and clinical trials of our product candidates. These operations provide a limited basis for you to assess our ability to commercialize our product candidates and the advisability of investing in our securities.

Because we currently neither have nor intend to establish internal research capabilities, we are dependent upon pharmaceutical and biotechnology companies and academic and other researchers to sell or license us their product candidates.

Proposing, negotiating, and implementing an economically viable product acquisition or license is a lengthy and complex process. We compete for partnering arrangements and license agreements with pharmaceutical, biopharmaceutical, and biotechnology companies, many of which have significantly more experience than we do, and have significantly more financial resources. Our competitors may have stronger relationships with certain third parties including academic research institutions, with whom we are interested in collaborating and may have, therefore, a competitive advantage in entering into partnering arrangements with those third parties. We may not be able to acquire rights to additional product candidates on terms that we find acceptable, or at all.

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We expect that any product candidate to which we acquire rights will require significant additional development and other efforts prior to commercial sale, including extensive clinical testing and approval by the FDA and applicable foreign regulatory authorities. All drug product candidates are subject to the risks of failure inherent in pharmaceutical product development, including the possibility that the product candidate will not be shown to be sufficiently safe or effective for approval by regulatory authorities. Even if our product candidates are approved, they may not be economically manufactured or produced, or be successfully commercialized.

We actively evaluate additional product candidates to acquire for development. Such additional product candidates, if any, could significantly increase our capital requirements and place further strain on the time of our existing personnel, which may delay or otherwise adversely affect the development of our existing product candidates. We must manage our development efforts and clinical trials effectively, and hire, train and integrate additional management, administrative, and sales and marketing personnel. We may not be able to accomplish these tasks, and our failure to accomplish any of them could prevent us from successfully growing our Company.

We may not be able to successfully manage our growth.

In the future, if we are able to advance our product candidates to the point of, and thereafter through, clinical trials, we will need to expand our development, regulatory, manufacturing, marketing and sales capabilities or contract with third parties to provide for these capabilities. Any future growth will place a significant strain on our management and on our administrative, operational, and financial resources. Therefore, our future financial performance and our ability to commercialize our product candidates and to compete effectively will depend, in part, on our ability to manage any future growth effectively. To manage this growth, we must expand our facilities, augment our operational, financial and management systems, and hire and train additional qualified personnel. If we are unable to manage our growth effectively, our business may be harmed.

Our business will subject us to the risk of liability claims associated with the use of hazardous materials and chemicals.

Our contract research and development activities may involve the controlled use of hazardous materials and chemicals. Although we believe that our safety procedures for using, storing, handling and disposing of these materials comply with federal, state and local laws and regulations, we cannot completely eliminate the risk of accidental injury or contamination from these materials. In the event of such an accident, we could be held liable for any resulting damages and any liability could have a materially adverse effect on our business, financial condition, and results of operations. In addition, the federal, state and local laws and regulations governing the use, manufacture, storage, handling and disposal of hazardous or radioactive materials and waste products may require our contractors to incur substantial compliance costs that could materially adversely affect our business, financial condition, and results of operations.

We rely on key executive officers and scientific and medical advisors, and their knowledge of our business and technical expertise would be difficult to replace.

We are highly dependent on Dr. Jonathan Lewis, our Chief Executive Officer and Chief Medical Officer, Richard Bagley, our President, Chief Operating Officer and Chief Financial Officer, and our principal scientific, regulatory,

and medical advisors. Dr. Lewis and Mr. Bagley s employment are governed by written employment agreements that provide for terms that expire in January 2013 and July 2011, respectively. Dr. Lewis and Mr. Bagley may terminate their employment with us at any time, subject, however, to certain non-compete and non-solicitation covenants. The loss of the technical knowledge and management and industry expertise of Dr. Lewis and Mr. Bagley, or any of our other key personnel, could result in delays in product development, loss of customers and sales, and diversion of management resources, which could adversely affect our operating results. We do not carry key person life insurance policies on any of our officers or key employees.

If we are unable to hire additional qualified personnel, our ability to grow our business may be harmed.

We will need to hire additional qualified personnel with expertise in preclinical and clinical research and testing, government regulation, formulation and manufacturing, and eventually, sales and marketing. We

We rely on key executive officers and scientific and medicaladvisors, and their knowledge of our business and tech

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compete for qualified individuals with numerous biopharmaceutical companies, universities, and other research institutions. Competition for such individuals is intense and we cannot be certain that our search for such personnel will be successful. Attracting and retaining qualified personnel will be critical to our success. If we are unable to hire additional qualified personnel, our ability to grow our business may be harmed.

We may incur substantial liabilities and may be required to limit commercialization of our products in response to product liability lawsuits.

The testing and marketing of medical products entail an inherent risk of product liability. If we cannot successfully defend ourselves against product liability claims, we may incur substantial liabilities or be required to limit commercialization of our products, if approved. Even a successful defense would require significant financial and management resources. Regardless of the merit or eventual outcome, liability claims may result in:

Decreased demand for our product candidates;
Injury to our reputation;
Withdrawal of clinical trial participants;
Withdrawal of prior governmental approvals;
Costs of related litigation;
Substantial monetary awards to patients;
Product recalls;
Loss of revenue; and
The inability to commercialize our product candidates.

We currently carry clinical trial insurance and product liability insurance. However, our inability to renew our policies or to obtain sufficient insurance at an acceptable cost could prevent or inhibit the commercialization of pharmaceutical products that we develop, alone or with collaborators.

Risks Related to the Clinical Testing, Regulatory Approval and Manufacturing of our Product Candidates

If we are unable to obtain the necessary U.S. or worldwide regulatory approvals to commercialize any product candidate, our business will suffer.

We may not be able to obtain the approvals necessary to commercialize our product candidates, or any product candidate that we may acquire or develop in the future for commercial sale. We will need FDA approval to commercialize our product candidates in the U.S. and approvals from regulatory authorities in foreign jurisdictions equivalent to the FDA to commercialize our product candidates in those jurisdictions. In order to obtain FDA approval of any product candidate, we must submit to the FDA a New Drug Application or Biologics License Application (BLA), demonstrating that the product candidate is safe for humans and effective for its intended use. This demonstration requires significant research and animal tests, which are referred to as preclinical studies, as well as human tests, which are referred to as clinical trials. Satisfaction of the FDA s regulatory requirements typically takes many years, depending upon the type, complexity, and novelty of the product candidate, and will require substantial

resources for research, development, and testing. We cannot predict whether our research, development, and clinical approaches will result in drugs that the FDA will consider safe for humans and effective for their intended uses. The FDA has substantial discretion in the drug approval process and may require us to conduct additional preclinical and clinical testing or to perform post-marketing studies. The approval process may also be delayed by changes in government regulation, future legislation, or administrative action or changes in FDA policy that occur prior to or during our regulatory review. Delays in obtaining regulatory approvals may:

Delay commercialization of, and our ability to derive product revenues from, our product candidates;
Impose costly procedures on us; and
Diminish any competitive advantages that we may otherwise enjoy.

If we are unable to obtain the necessary U.S. or worldwideregulatory approvals to commercialize any product candi

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Even if we comply with all FDA requests, the FDA may ultimately reject one or more of our NDAs or BLAs. We cannot be sure that we will ever obtain regulatory clearance for any of our product candidates. Although individuals within Ziopharm have experience working with biologic product candidates, to date we as a company have not had any interactions with FDA s Center for Biologics Evaluation and Research, and our submission of the IND for INXN 2001/1001 will be our first biologic IND. Failure to obtain FDA approval for our product candidates will severely undermine our business by leaving us without a saleable product, and therefore without any potential revenue source, until another product candidate can be developed. There is no guarantee that we will ever be able to develop or acquire another product candidate or that we will obtain FDA approval if we are able to do so.

In foreign jurisdictions, we similarly must receive approval from applicable regulatory authorities before we can commercialize any drugs. Foreign regulatory approval processes generally include all of the risks associated with the FDA approval procedures described above.

Our product candidates are in various stages of clinical trials, which are very expensive and time-consuming. We cannot be certain when we will be able to submit an NDA or BLA to the FDA and any failure or delay in completing clinical trials for our product candidates could harm our business.

Our product candidates are in various stages of development and require extensive clinical testing. Notwithstanding our current clinical trial plans for each of our existing product candidates, we may not be able to commence additional trials or see results from these trials within our anticipated timelines. As such, we cannot predict with any certainty if or when we might submit an NDA for regulatory approval of our product candidates or whether such an NDA will be accepted. Because we do not anticipate generating revenues unless and until we submit one or more NDAs and thereafter obtain requisite FDA approvals, the timing of our NDA submissions and FDA determinations regarding approval thereof, will directly affect if and when we are able to generate revenues.

The results of our clinical trials may not support our product candidate claims.

Even if our clinical trials are completed as planned, we cannot be certain that their results will support approval of our product candidates. FDA normally expects two randomized, well controlled Phase 3 pivotal studies in support of approval of an NDA or BLA. Our PICASSO 3 trial, even if successful, may not be sufficient to support approval and we may be required to conduct additional pivotal trials of palifosfamide in soft tissue sarcoma in order to obtain NDA approval. Success in preclinical testing and early clinical trials does not ensure that later clinical trials will be successful, and we cannot be certain that the results of later clinical trials will replicate the results of prior clinical trials and preclinical testing. The clinical trial process may fail to demonstrate that our product candidates are safe for humans and effective for the indicated uses. This failure would cause us to abandon a product candidate and may delay development of other product candidates. Any delay in, or termination of, our clinical trials will delay the submission of our NDAs or BLAs with the FDA and, ultimately, our ability to commercialize our product candidates and generate product revenues. In addition, our clinical trials involve small patient populations. Because of the small sample size, the results of these clinical trials may not be indicative of future results.

Because we are dependent upon clinical research institutions and other contractors for clinical testing and for research and development activities, the results of our clinical trials and such research activities are, to a certain extent, beyond our control.

We materially rely upon independent investigators and collaborators, such as universities and medical institutions, to conduct our preclinical and clinical trials under agreements with us. These collaborators are not our employees and we cannot control the amount or timing of resources that they devote to our programs. These investigators may not assign as great a priority to our programs or pursue them as diligently as we would if we were undertaking such programs ourselves. If outside collaborators fail to devote sufficient time and resources to our drug development programs, or if their performance is substandard, the approval of our FDA applications, if any, and our introduction of new products, if any, will be delayed. These collaborators may also have relationships with other commercial entities, some of whom may compete with us. If our collaborators assist our competitors to our detriment, our competitive position would be harmed.

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Our reliance on third parties to formulate and manufacture our product candidates exposes us to a number of risks that may delay the development, regulatory approval and commercialization of our products or result in higher product costs.

We do not have experience in drug formulation or manufacturing of drugs or biologics and do not intend to establish our own manufacturing facilities. Although we will work closely with and rely upon Intrexon on the manufacturing and scale-up of Intrexon product candidates, we lack the resources and expertise to formulate or manufacture our own product candidates. We currently are contracting for the manufacture of our product candidates. We intend to contract with one or more manufacturers to manufacture, supply, store, and distribute drug supplies for our clinical trials. If a product candidate we develop or acquire in the future receives FDA approval, we will rely on one or more third-party contractors or Intrexon to manufacture our products. Our anticipated future reliance on a limited number of third-party manufacturers exposes us to the following risks:

We may be unable to identify manufacturers on acceptable terms or at all because the number of potential manufacturers is limited and the FDA must approve any replacement contractor. This approval would require new testing and compliance inspections. In addition, a new manufacturer would have to be educated in, or develop substantially equivalent processes for, production of our products after receipt of FDA approval, if any.

Our third-party manufacturers might be unable to formulate and manufacture our products in the volume and of the quality required to meet our clinical needs and commercial needs, if any.

Our future contract manufacturers may not perform as agreed or may not remain in the contract manufacturing business for the time required to supply our clinical trials or to successfully produce, store, and distribute our products.

Drug manufacturers are subject to ongoing periodic unannounced inspection by the FDA, the Drug Enforcement Administration and corresponding state agencies to ensure strict compliance with good manufacturing practices and other government regulations and corresponding foreign standards. We do not have control over third-party manufacturers compliance with these regulations and standards.

If any third-party manufacturer makes improvements in the manufacturing process for our products, we may not own, or may have to share, the intellectual property rights to the innovation.

Each of these risks could delay our clinical trials, the approval, if any, of our product candidates by the FDA or the commercialization of our product candidates or result in higher costs or deprive us of potential product revenues.

Risks Related to our Ability Commercialize Our Product Candidates

If we are unable either to create sales, marketing and distribution capabilities or enter into agreements with third parties to perform these functions, we will be unable to commercialize our product candidates successfully.

We currently have no marketing, sales, or distribution capabilities. If and when we become reasonably certain that we will be able to commercialize our current or future products, we anticipate allocating resources to the marketing, sales and distribution of our proposed products in North America and in certain other countries; however, we cannot assure that we will be able to market, sell, and distribute our products successfully. Our future success also may depend, in part, on our ability to enter into and maintain collaborative relationships for such capabilities and to encourage the collaborator s strategic interest in the products under development, and such collaborator s ability to successfully market and sell any such products. Although we intend to pursue certain collaborative arrangements regarding the sale and marketing of certain of our products, there are no assurances that we will be able to establish or maintain collaborative arrangements or, if we are able to do so, whether we would be able to conduct our own sales efforts. There can also be no assurance that we will be able to establish or maintain relationships with third-party collaborators or develop in-house sales and distribution capabilities. To the extent that we depend on third parties for marketing and distribution, any revenues we receive will depend upon the efforts of such third parties, and there can be no assurance that such efforts will be successful. In addition, there can also be no assurance that we will be able to market and sell our products in the United States or overseas.

If we are unable either to create sales, marketing anddistribution capabilities or enter into agreements with thirdpart

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If we are not able to partner with a third party and are not successful in recruiting sales and marketing personnel or in building a sales and marketing infrastructure, we will have difficulty commercializing our product candidates, which would harm our business. If we rely on pharmaceutical or biotechnology companies with established distribution systems to market our products, we will need to establish and maintain partnership arrangements, and we may not be able to enter into these arrangements on acceptable terms or at all. To the extent that we enter into co-promotion or other arrangements, any revenues we receive will depend upon the efforts of third parties that may not be successful and that will be only partially in our control.

If we cannot compete successfully for market share against other drug companies, we may not achieve sufficient product revenues and our business will suffer.

The market for our product candidates is characterized by intense competition and rapid technological advances. If a product candidate receives FDA approval, it will compete with a number of existing and future drugs and therapies developed, manufactured and marketed by others. Existing or future competing products may provide greater therapeutic convenience or clinical or other benefits for a specific indication than our products, or may offer comparable performance at a lower cost. If our products fail to capture and maintain market share, we may not achieve sufficient product revenues and our business will suffer.

We will compete against fully integrated pharmaceutical companies and smaller companies that are collaborating with larger pharmaceutical companies, academic institutions, government agencies and other public and private research organizations. Many of these competitors have products already approved or in development. In addition, many of these competitors, either alone or together with their collaborative partners, operate larger research and development programs or have substantially greater financial resources than we do, as well as significantly greater experience in:

Developing drugs and biopharmaceuticals;
Undertaking preclinical testing and human clinical trials;
Obtaining FDA and other regulatory approvals of drugs and biopharmaceuticals;
Formulating and manufacturing drugs and biopharmaceuticals; and
Launching, marketing, and selling drugs and biopharmaceuticals.

If physicians and patients do not accept and use our product candidates, our ability to generate revenue from sales of our products will be materially impaired.

Even if the FDA approves our product candidates, physicians and patients may not accept and use them. Acceptance and use of our products will depend upon a number of factors including:

Perceptions by members of the health care community, including physicians, about the safety and effectiveness of our products;
Pharmacological benefit and cost-effectiveness of our products relative to competing products;
Availability of reimbursement for our products from government or other healthcare payors;
Effectiveness of marketing and distribution efforts by us and our licensees and distributors, if any; and
The price at which we sell our products.

Because we expect sales of our current product candidates, if approved, to generate substantially all of our product

revenues for the foreseeable future, the failure of a drug to find market acceptance would harm our business and could require us to seek additional financing in order to fund the development of future product candidates.

Our ability to generate product revenues will be diminished if our products sell for inadequate prices or patients are unable to obtain adequate levels of reimbursement.

Our ability to commercialize our drugs, alone or with collaborators, will depend in part on the extent to which reimbursement will be available from:

If physicians and patients do not accept and use our productcandidates, our ability to generate revenue from sales

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Government and health administration authorities;
Private health maintenance organizations and health insurers; and
Other healthcare payers.

Government and other healthcare payers increasingly attempt to contain healthcare costs by limiting both coverage and the level of reimbursement for drugs. As a result, we cannot provide any assurances that third-party payors will provide adequate coverage of and reimbursement for any of our product candidates. If we are unable to obtain adequate coverage of and payment levels for our product candidates from third-party payors, physicians may limit how much or under what circumstances they will prescribe or administer them and patients may decline to purchase them. This in turn could affect our ability to successfully commercialize our products and impact our profitability and future success.

In both the United States and certain foreign jurisdictions, there have been a number of legislative and regulatory proposals and changes in recent years to change the healthcare system in ways that could impact our ability to sell our products profitably.

We cannot predict the impact on our business of any legislation or regulations that may be adopted in the future. The implementation of cost containment measures or other healthcare reforms may prevent us from being able to generate revenue, attain profitability, or commercialize our products.

In addition, in many foreign countries, particularly the countries of the European Union, the pricing of prescription drugs is subject to government control. We may face competition for our product candidates from lower-priced products in foreign countries that have placed price controls on pharmaceutical products. In addition, there may be importation of foreign products that compete with our own products, which could negatively impact our profitability.

Risks Related to Our Intellectual Property

If we fail to adequately protect or enforce our intellectual property rights or secure rights to patents of others, the value of our intellectual property rights would diminish.

Our success, competitive position, and future revenues will depend in part on our ability and the abilities of our licensors to obtain and maintain patent protection for our products, methods, processes and other technologies, to preserve our trade secrets, to prevent third parties from infringing on our proprietary rights, and to operate without infringing the proprietary rights of third parties.

To date, we have exclusive rights to certain U.S. and foreign intellectual property with respect to our small molecule product candidates but are dependent on Intrexon s filings with respect to the existing Intrexon product candidates. Per the Channel Partner agreement, Intrexon has the sole right to control the filings, prosecution and maintenance of the Channel Program patents and applications. Although Intrexon has agreed to consider our comments regarding Channel Program patents and patent applications, we cannot guarantee that our comments will be solicited or followed. Without direct control of the Channel Program patents and patent applications, we are dependent on Intrexon to keep us advised of prosecution, particularly in foreign jurisdictions where prosecution information may not be publicly available. We anticipate that we and Intrexon will file additional patent applications both in the U.S. and in other countries. However, we cannot predict or guarantee:

The degree and range of protection any patents will afford us against competitors, including whether third parties will find ways to invalidate or otherwise circumvent our patents;

If and when patents will be issued;

Whether or not others will obtain patents claiming aspects similar to those covered by our patents and patent applications; or

Whether we will need to initiate litigation or administrative proceedings that may be costly whether we win or lose.

Certain technologies utilized in our research and development programs are already in the public domain. Moreover, a number of our competitors have developed technologies, filed patent applications or obtained

If we fail to adequately protect or enforce our intellectualproperty rights or secure rights to patents of others, the valu

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patents on technologies, compositions and methods of use that are related to our business and may cover or conflict with our patent applications, technologies or product candidates. Such conflicts could limit the scope of the patents that we may be able to obtain or may result in the denial of our patent applications. In addition, our own earlier filed patents and applications or those of Intrexon may limit the scope of later patents we obtain or may result in the denial of our later filed patent applications. If third parties filed patent applications or obtained patents on technologies, compositions and methods of use that are related to our business and that cover or conflict with our patent applications, technologies or product candidates, we may be required to challenge such protection, terminate or modify our programs impacted by such protection or obtain licenses from such third parties, which might not be available on acceptable terms, or at all.

Our success also depends upon the skills, knowledge, and experience of our scientific and technical personnel, our consultants and advisors, as well as our licensors and contractors. To help protect our proprietary know-how and our inventions for which patents may be unobtainable or difficult to obtain, we rely on trade secret protection and confidentiality agreements. To this end, it is our general policy to require our employees, consultants, advisors, and contractors to enter into agreements that prohibit the disclosure of confidential information and, where applicable, require disclosure and assignment to us of the ideas, developments, discoveries, and inventions important to our business. These agreements may not provide adequate protection for our trade secrets, know-how or other proprietary information in the event of any unauthorized use or disclosure or the lawful development by others of such information. If any of our trade secrets, know-how or other proprietary information is disclosed, the value of our trade secrets, know-how and other proprietary rights would be significantly impaired and our business and competitive position would suffer.

Third-party claims of intellectual property infringement would require us to spend significant time and money and could prevent us from developing or commercializing our products.

In order to protect or enforce patent rights, we or Intrexon may initiate patent litigation against third parties. Similarly, we may be sued by others. We also may become subject to proceedings conducted in the U.S. Patent and Trademark Office, including interference proceedings to determine the priority of inventions, or reexamination proceedings. In addition, any foreign patents that are granted may become subject to opposition, nullity, or revocation proceedings in foreign jurisdictions having such proceedings. The defense and prosecution, if necessary, of intellectual property actions are costly and divert technical and management personnel away from their normal responsibilities.

No patent can protect its holder from a claim of infringement of another patent. Therefore, our patent position cannot and does not provide any assurance that the commercialization of our products would not infringe the patent rights of another. While we know of no actual or threatened claim of infringement that would be material to us, there can be no assurance that such a claim will not be asserted.

If such a claim is asserted, there can be no assurance that the resolution of the claim would permit us to continue marketing the relevant product on commercially reasonable terms, if at all. We may not have sufficient resources to bring these actions to a successful conclusion. If we do not successfully defend any infringement actions to which we become a party or are unable to have infringed patents declared invalid or unenforceable, we may have to pay substantial monetary damages, which can be tripled if the infringement is deemed willful, or be required to discontinue or significantly delay commercialization and development of the affected products.

Any legal action against us or our collaborators claiming damages and seeking to enjoin developmental or marketing activities relating to affected products could, in addition to subjecting us to potential liability for damages, require us or our collaborators to obtain licenses to continue to develop, manufacture, or market the affected products. Such a license may not be available to us on commercially reasonable terms, if at all.

An adverse determination in a proceeding involving our owned or licensed intellectual property may allow entry of generic substitutes for our products.

Third-party claims of intellectual property infringement would require us to spend significant time and money and co

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Other Risks Related to Our Company

We are subject to Sarbanes-Oxley and the reporting requirements of federal securities laws, which can be expensive.

As a public reporting company, we are subject to the Sarbanes-Oxley Act of 2002, as well as to the information and reporting requirements of the Securities Exchange Act of 1934, as amended, and other federal securities laws. As a result, we incur significant legal, accounting, and other expenses that we did not incur as a private company, including costs associated with our public company reporting requirements and corporate governance requirements. As an example of public reporting company requirements, we evaluate the effectiveness of disclosure controls and procedures and of our internal control over financing reporting in order to allow management to report on such controls. Sarbanes-Oxley generally requires that a public reporting company s independent registered public accounting firm attest to the effectiveness of the company s internal control over financial reporting as of the end of each fiscal year in the company s Annual Report on Form 10-K. While our management has not currently identified any material weaknesses in our internal control over financial reporting, there can be no assurance that we will not identify identified any material weaknesses during the current year or that our systems will be deemed effective when our independent registered public accounting firm reviews the systems during 2010 and tests transactions. In addition, any updates to our finance and accounting systems, procedures and controls, which may be required as a result of our ongoing analysis of internal controls, or results of testing by our independent auditor, may require significant time and expense.

Management is working to continuously monitor and improve internal controls and has set in place controls to mitigate the potential segregation of duties risk. In the event significant deficiencies or material weaknesses are indentified in our internal control over financial reporting that we cannot remediate in a timely manner, investors and others may lose confidence in the reliability of our financial statements and the trading price of our common stock and ability to obtain any necessary equity or debt financing could suffer. In addition, in the event that our independent registered public accounting firm is unable to rely on our internal controls over financial reporting in connection with its audit of our financial statements, and in the further event that it is unable to devise alternative procedures in order to satisfy itself as to the material accuracy of our financial statements and related disclosures, we may be unable to file our periodic reports with the Securities and Exchange Commission. This would likely have an adverse affect on the trading price of our common stock and our ability to secure any necessary additional equity or debt financing, and could result in the delisting of our common stock from the NASDAQ Capital Market, which would severely limit the liquidity of our common stock.

Anti-takeover provisions in our charter documents and under Delaware law may make an acquisition of us, which may be beneficial to our stockholders, more difficult.

Provisions of our amended and restated certificate of incorporation and bylaws, as well as provisions of Delaware law, could make it more difficult for a third party to acquire us, even if doing so would benefit our stockholders. These provisions authorize the issuance of blank check preferred stock that could be issued by our board of directors to increase the number of outstanding shares and hinder a takeover attempt, and limit who may call a special meeting of stockholders. In addition, we are subject to Section 203 of the Delaware General Corporation Law. In general, this statute prohibits a publicly-held Delaware corporation from engaging in a business combination with a party that owns

at least 15% of its common stock unless the business combination is approved by the company s board of directors before the person acquires the 15% ownership stake or later by its board of directors and two-thirds of its stockholders. In connection with our January 12, 2011 issuance of shares of common stock to Intrexon Corporation in a private placement transaction (*see Recent Developments Intrexon Corporation Private Placement and Equity Commitment*), our board of directors waived the Section 203 prohibition with respect to a future business combination with Intrexon Corporation. However, the Stock Purchase Agreement governing such issuance contains a standstill provision that generally prohibits Intrexon from seeking, initiating, offering or proposing to effect such a transaction with our inviting them to do so. Section 203 and this standstill provision could have the effect of delaying, deferring or preventing a change in control that our stockholders might consider to be in their best interests.

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Because we do not expect to pay dividends, you will not realize any income from an investment in our common stock unless and until you sell your shares at a profit.

We have never paid dividends on our capital stock and we do not anticipate that we will pay any dividends for the foreseeable future. Accordingly, any return on an investment in our Company will be realized, if at all, only when you sell shares of our common stock.

SPECIAL NOTE REGARDING FORWARD-LOOKING STATEMENTS

This prospectus supplement and the accompanying prospectus contain, and the documents incorporated by reference herein and therein and any free writing prospectus that we have authorized for use in connection with this offering may contain, forward-looking statements within the meaning of Section 27A of the Securities Act of 1933, as amended, or the Securities Act, and Section 21E of the Securities Exchange Act of 1934, as amended, or the Exchange Act. These statements relate to future events or to our future operating or financial performance and involve known and unknown risks, uncertainties and other factors which may cause our actual results, performance or achievements to be materially different from any future results, performances or achievements expressed or implied by the forward-looking statements. Forward-looking statements may include, but are not limited to statements about:

the progress, timing and results of preclinical and clinical trials involving our drug candidates;
the progress of our research and development programs;
our plans or others plans to conduct future clinical trials or research and development efforts;
the risk that final trial data may not support interim analysis of the viability of our drug candidates;
our plans and expectations regarding partnering our drug candidates;
the benefits to be derived from relationships with our collaborators;
the receipt or anticipated receipt of regulatory clearances and approvals;
estimates of the potential markets for our drug candidates;
our ability to adequately protect our intellectual property rights;
the use of proceeds from this offering;
our estimates of future revenues and profitability; and
our estimates regarding our capital requirements, our ability to control our costs and our need for additional funding.

In some cases, you can identify forward-looking statements by terms such as may , will , should , could , would , plans , anticipates , believes , estimates , projects , predicts , potential and similar expressions intended to forward-looking statements. These statements reflect our current views with respect to future events and are based on assumptions and subject to risks and uncertainties. Given these uncertainties, you should not place undue reliance on these forward-looking statements. We discuss many of these risks in greater detail under the heading Risk Factors beginning on page S-9 of this prospectus supplement and in our SEC filings. Also, these forward-looking statements represent our estimates and assumptions only as of the date of the document containing the applicable statement.

You should read this prospectus supplement, the accompanying prospectus, the documents we have filed with the SEC that are incorporated by reference and any free writing prospectus that we have authorized for use in connection with this offering completely and with the understanding that our actual future results may be materially different from what we expect. We qualify all of the forward-looking statements in the foregoing documents by these

cautionary statements.

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You should rely only on the information contained, or incorporated by reference, in this prospectus supplement, the accompanying prospectus and any free writing prospectus that we have authorized for use in connection with this offering. We and the underwriter for this offering have not authorized anyone to provide you with different information. The common stock offered under this prospectus is not being offered in any state where the offer is not permitted. You should not assume that the information contained in this prospectus supplement or the accompanying prospectus is accurate as of any date other than the date on the front of this prospectus supplement or the accompanying prospectus, as applicable, or that any information incorporated by reference in this prospectus supplement or the accompanying prospectus is accurate as of any date other than the date of the document so incorporated by reference. Unless required by law, we undertake no obligation to update or revise any forward-looking statements to reflect new information or future events or developments. Thus, you should not assume that our silence over time means that actual events are bearing out as expressed or implied in such forward-looking statements.

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USE OF PROCEEDS

We estimate that the net proceeds from the sale of the 9,600,000 shares of common stock that we are offering will be approximately $51.6 million, or approximately $59.4 million if the underwriter exercises in full its option to purchase an additional 1,440,000 shares of common stock, based on the public offering price of $5.75 per share and after deducting the underwriting discounts and commissions and estimated offering expenses payable by us.

We intend to use the net proceeds from this public offering for the overall development of our drug candidates, including to further expand the clinical trial programs, and for general corporate and working capital purposes.

The amounts and timing of these expenditures will depend on a number of factors, such as the timing and progress of our research and development efforts, the timing and progress of any partnering efforts, technological advances and the competitive environment for our product candidates. As of the date of this prospectus supplement, we cannot specify with certainty all of the particular uses for the net proceeds to us from this offering. Accordingly, our management will have broad discretion in the application of these proceeds. Pending application of the net proceeds as described above, we intend to invest the proceeds in investment grade interest bearing instruments.

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DILUTION

Our net tangible book value as of September 30, 2010 was approximately $42.2 million, or $0.87 per share. Net tangible book value per share is determined by dividing our total tangible assets, less total liabilities, by the number of shares of our common stock outstanding as of September 30, 2010. Dilution in net tangible book value per share represents the difference between the amount per share paid by purchasers of shares of common stock in this public offering and the net tangible book value per share of our common stock immediately after this public offering.

After giving effect to the sale of 9,600,000 shares of our common stock in this offering at the public offering price of $5.75 per share, and after deducting underwriting discounts and commissions and estimated offering expenses payable by us, and taking into account our January 12, 2011 issuance and sale of common stock to Intrexon Corporation, our as adjusted net tangible book value as of September 30, 2010 would have been approximately $105.4 million, or $1.64 per share. This represents an immediate increase in net tangible book value of $0.65 per share to existing stockholders and an immediate dilution of $4.11 per share to investors purchasing our common stock in this offering at the public offering price. The following table illustrates this dilution on a per share basis:

Public offering price per share		$ 5.75
Net tangible book value per share as of September 30, 2010	$ 0.87	
Pro forma increase in tangible book value per share attributable to the January 12, 2011 sale and issuance of 6,063,161 shares of common stock to Intrexon Corporation in a private placement transaction for a purchase price of approximately $11.6 million	$ 0.12	
Increase per share attributable to investors purchasing our common stock in this offering	$ 0.65	
As adjusted net tangible book value per share as of September 30, 2010, after giving effect to this offering		$ 1.64
Dilution in net tangible book value per share to investors purchasing our common stock in this offering		$ 4.11

If the underwriter exercises in full their option to purchase 1,440,000 additional shares of common stock at the public offering price of $5.75 per share, the pro forma as adjusted net tangible book value after this offering would be $1.73 per share, representing an increase in net tangible book value of $0.74 per share to existing stockholders and an immediate dilution in net tangible book value of $4.02 per share to investors purchasing our common stock in this offering at the public offering price.

The amounts above are based on 48,557,678 shares of common stock outstanding as of September 30, 2010 and assume no exercise of outstanding options or warrants since that date. The number of common stock expected to be outstanding after this offering excludes:

- 3,528,852 shares of our common stock issuable upon the exercise of outstanding stock options as of September 30, 2010, including those issued under our 2003 Stock Option Plan, having a weighted average exercise price of $3.02 per share;
- 3,074,734 additional shares of our common stock reserved for future issuance as of September 30, 2010 under our 2003 Stock Option Plan; and
- 15,924,642 shares of our common stock issuable upon the exercise of outstanding warrants as of September 30, 2010 with a weighted-average exercise price of $4.11 per share.

To the extent options or warrants outstanding as of September 30, 2010 have been or may be exercised or other shares have been issued, there may be further dilution to investors.

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MATERIAL U.S. FEDERAL INCOME AND ESTATE TAX CONSEQUENCES FOR CERTAIN NON-U.S. HOLDERS

The following summary describes the material U.S. federal income and estate tax consequences of the acquisition, ownership and disposition of our common stock acquired in this offering by a Non-U.S. Holder (as defined below). This discussion does not address all aspects of U.S. federal income and estate taxes and does not deal with foreign, state and local consequences that may be relevant to Non-U.S. Holders in light of their particular circumstances. Special rules 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, partnerships a other pass-through entities, and investors in such pass-through entities. 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 and estate tax consequences different from those discussed below. This discussion assumes that the Non-U.S. Holder holds our common stock as a capital asset.

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

Except as otherwise described in the discussion of estate tax below, a Non-U.S. Holder is a beneficial holder of our common stock that is not a U.S. Holder or a partnership. A U.S. Holder means a beneficial holder of our common stock that is for U.S. federal income tax purposes (i) an individual who is a citizen or resident of the United States, (ii) a corporation or other entity treated as a corporation created or organized in or under the laws of the United States or any political subdivision thereof, (iii) an estate the income of which is subject to U.S. federal income taxation regardless of its source or (iv) a trust if it (x) 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 (y) has a valid election in effect under applicable U.S. Treasury regulations to be treated as a U.S. person.

If a partnership (including any entity or arrangement treated as a partnership for U.S. federal income tax purposes) acquires our common stock, the tax treatment of a partner in the partnership will generally depend upon the status of the partner and the activities of the partnership. Persons who are partners of partnerships holding our common stock are urged to consult their tax advisors.

Distributions

Subject to the discussion below, distributions, if any, made to a Non-U.S. Holder of our common stock out of our current or accumulated earnings and profits 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. Treasury regulations provide special rules to determine whether, for purposes of determining the applicability of a tax treaty, dividends paid to a Non-U.S. Holder that is an entity should 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.

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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 if a properly-executed IRS Form W-8ECI, stating that the dividends are so connected (and are not exempt from net U.S. federal income tax under a treaty as described below), is filed with us. Effectively connected dividends will be subject to net U.S. federal income tax, generally in the same manner and at the regular rate as if the Non-U.S. Holder were a U.S. citizen or resident alien or a domestic corporation, as the case may be, unless a specific treaty exemption applies. If the Non-U.S. Holder is eligible for the benefits of a tax treaty between the United States and the holder s country of residence, any effectively connected dividends would generally be subject to net U.S. federal income tax only if they are also attributable to a permanent establishment maintained by the holder in the United States. 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) of the corporate Non-U.S. Holder s effectively connected earnings and profits, subject to certain adjustments. If you are eligible for a reduced rate of withholding tax pursuant to a tax treaty, you may generally obtain a refund of any excess amounts currently withheld if you timely file an appropriate claim for refund with the IRS.

To the extent distributions on our common stock, if any, exceed our current and accumulated earnings and profits, they will constitute a return of capital and will first reduce your basis in our common stock, but not below zero, and then will be treated as gain from the sale of stock.

Gain on Disposition of Common Stock

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 (i) the gain is effectively connected with a trade or business of such holder in the United States, (ii) in the case of Non-U.S. Holders who are nonresident alien individuals, such individuals are present in the United States for 183 or more days in the taxable year of the disposition and certain other conditions are met, or (iii) we are or have been a United States real property holding corporation within the meaning of Code Section 897(c)(2) at any time within the shorter of the five-year period preceding such disposition or such holder s holding period. In general, we would be a United States real property holding corporation if interests in U.S. real estate comprised at least half of our business assets. We believe that we are not, and do not anticipate becoming, a United States real property holding corporation. Even if we are treated as a United States real property holding corporation, gain realized by a Non-U.S. Holder on a disposition of our common stock will not be subject to U.S. federal income tax so long as (1) the Non-U.S. Holder owned directly, indirectly and constructively, no more than five percent of our common stock at all times within the shorter of (a) the five year period preceding the disposition or (b) the holder s holding period and (2) our common stock is regularly traded on an established securities market. There can be no assurance that our common stock will continue to qualify as regularly traded on an established securities market.

If you are a Non-U.S. Holder described in (i) above, you will be required to pay tax on the net gain derived from the sale at generally applicable United States federal income tax rates, subject to an applicable income tax treaty providing otherwise, and corporate Non-U.S. Holders described in (i) above may be subject to the 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 (ii) above, you will be required to pay a flat 30% tax (or a reduced rate under an applicable income tax treaty) on the gain derived from the sale, which tax may be offset by U.S. source capital losses if you have timely filed tax returns with respect to such losses (even though you are not considered a resident of the United States). If gain realized by you on the sale of our common stock is taxable because we are a United States real property holding corporation and your ownership of our common stock exceeded the 5% threshold in the period noted above, you will be taxed on such disposition generally in the manner applicable to U.S. persons.

Information Reporting Requirements and Backup Withholding

Generally, we must report information to the IRS with respect to any dividends we pay on our 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.

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Proceeds from a disposition of our stock and 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. The current backup withholding rate is 28%. Notwithstanding the foregoing, backup withholding may apply if either we or our paying agent has actual knowledge, or reason to know, that the holder of our common stock is a U.S. person that is not an exempt recipient.

Backup withholding is not an additional tax. Rather, the tax liability of persons subject to backup withholding will be reduced by the amount of tax withheld. If withholding results in an overpayment of taxes, a refund may generally be obtained, provided that the required information is timely furnished to the IRS.

New legislation relating to foreign accounts

Newly enacted legislation may impose withholding taxes on certain types of payments made to foreign financial institutions (as specifically defined in this new legislation) and certain other non-U.S. entities (including financial intermediaries). Under this legislation, the failure to comply with additional certification, information reporting and other specified requirements could result in withholding tax being imposed on payments of dividends and sales proceeds to foreign intermediaries and certain Non-U.S. Holders. The legislation imposes a 30% withholding tax on dividends, or gross proceeds from the sale or other disposition of, common stock paid to a foreign financial institution or to a foreign non-financial entity, unless (i) the foreign financial institution undertakes certain diligence and reporting obligations or (ii) the foreign non-financial entity either certifies it does not have any substantial United States owners or furnishes identifying information regarding each substantial United States owner. If the payee is a foreign financial institution, it must enter into an agreement with the United States Treasury requiring, among other things, that it undertake to identify accounts held by certain United States persons or United States-owned foreign entities, annually report certain information about such accounts, and withhold 30% on payments to account holders whose actions prevent it from complying with these reporting and other requirements. The legislation applies to payments made after December 31, 2012. Prospective investors should consult their tax advisors regarding this legislation.

Federal estate tax

Common stock owned or treated as owned by an individual who is not a citizen or resident of the United States (as specifically defined for U.S. federal estate tax purposes) at the time of death is considered a U.S. situs asset includible in the individual s gross estate for U.S. federal estate tax purposes and therefore may be subject to U.S. federal estate tax, unless an applicable estate tax treaty provides otherwise. Prospective investors are urged to consult their tax advisors regarding the U.S. federal estate tax considerations of acquiring, holding, and disposing of common stock. The test for whether an individual is a resident of the United States for federal estate tax purposes differs from the test used for U.S. federal income tax purposes. Some individuals, therefore, may be Non-U.S. Holders for U.S. federal income tax purposes, but not for U.S. federal estate tax purposes, and vice versa.

THE PRECEDING DISCUSSION OF 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.

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UNDERWRITING

Under the terms of an underwriting agreement, which we will file as an exhibit to our current report on Form 8-K and incorporate by reference in this prospectus supplement and the accompanying prospectus, Barclays Capital Inc., as the underwriter in this offering, has agreed to purchase from us, 9,600,000 shares of common stock.

The underwriting agreement provides that the underwriter s obligation to purchase shares of common stock depends on the satisfaction of the conditions contained in the underwriting agreement including:

the obligation to purchase all of the shares of common stock offered hereby (other than those shares of common stock covered by their option to purchase additional shares as described below), if any of the shares are purchased;

the representations and warranties made by us to the underwriter are true;

there is no material change in our business or in the financial markets; and

we deliver customary closing documents to the underwriter.

Commissions and Expenses

The following table summarizes the underwriting discounts and commissions we will pay to the underwriter. Such amounts are shown assuming both no exercise and full exercise of the underwriter s option to purchase additional shares. The underwriting fee is the difference between the initial price to the public and the amount the underwriter pays to us for the shares.

	Per Share		Total	
	Without Option to Purchase Additional Shares	With Option to Purchase Additional Shares	Without Option to Purchase Additional Shares	With Option to Purchase Additional Shares
Public offering price	$5.75	$ 5.75	$55,200,000	$63,480,000
Underwriting discounts and commissions paid by us	$0.325	$ 0.325	$3,120,000	$3,588,000

The underwriter has advised us that it proposes to offer the shares of common stock directly to the public at the public offering price on the cover of this prospectus supplement and to selected dealers, which may include the underwriter, at such offering price less a selling concession not in excess of $0.20 per share. After the offering, the underwriter may change the offering price and other selling terms. Sales of shares made outside of the United States may be made by affiliates of the underwriter.

The expenses of the offering that are payable by us are estimated to be $500,000 (excluding underwriting discounts and commissions).

Option to Purchase Additional Shares

If the underwriter sells more shares than the total number set forth above, we have granted to the underwriter an option, exercisable for 30 days from the date of this prospectus supplement, to purchase up to 1,440,000 additional shares. The underwriter may exercise the option solely for the purpose of covering over-allotments, if any, in

connection with this offering. Any shares issued or sold under the option will be issued and sold on the same terms and conditions as the other shares that are the subject of this offering.

Lock-Up Agreements

We, all of our directors and executive officers, and certain of our stockholders have agreed that, subject to certain exceptions, without the prior written consent of Barclays Capital Inc., we and they will not directly or indirectly (1) offer for sale, sell, pledge, or otherwise dispose of (or enter into any transaction or device that is designed to, or could be expected to, result in the disposition by any person at any time in the future of) any shares of common stock (including, without limitation, shares of common stock that may be deemed to be beneficially owned in accordance with the rules and regulations of the Securities and Exchange Commission and shares of common stock that may be issued upon exercise of any options or warrants) or

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securities convertible into or exercisable or exchangeable for common stock, (2) enter into any swap or other derivatives transaction that transfers to another, in whole or in part, any of the economic consequences of ownership of the common stock, (3) make any demand for or exercise any right or file or cause to be filed a registration statement, including any amendments thereto, with respect to the registration of any shares of common stock or securities convertible, exercisable or exchangeable into common stock or any of our other securities, or (4) publicly disclose the intention to do any of the foregoing for a period of 90 days after the date of this prospectus supplement.

The 90-day restricted period described in the preceding paragraph will be extended if:

during the last 17 days of the 90-day restricted period we issue an earnings release or material news or a material event relating to us occurs; or

prior to the expiration of the 90-day restricted period, we announce that we will release earnings results during the 16-day period beginning on the last day of the 90-day period;

in which case the restrictions described in the preceding paragraph will continue to apply until the expiration of the 18-day period beginning on the issuance of the earnings release or the announcement of the material news or occurrence of material event, , unless Barclays Capital Inc. waives such extension in writing; except that such extension will not apply if (i) the shares of common stock are actively traded securities (as defined in Regulation M under the Securities Exchange Act of 1934, as amended, or the Exchange Act), (ii) we meet the applicable requirements of paragraph (a)(1) of Rule 139 under the Securities Act in the manner contemplated by NASD Conduct Rule 2711(f)(4), and (iii) the provisions of NASD Conduct Rule 2711(f)(4) do not restrict the publishing or distribution of any research reports relating to us published or distributed by the Underwriter during the 15 days before or after the last day of the 90-day restricted period (before giving effect to such extension).

Notwithstanding the foregoing, Barclays Capital Inc., has agreed that the transfer restrictions shall not apply to:

with respect to us, (a) any sales pursuant to this offering; (b) the issuance of shares of our common stock issued upon the settlement, vesting or exercise of options, warrants or rights outstanding in place at the time of the offering; (c) subject to certain limitations, the issuance of any shares or rights to purchase our common stock issued pursuant to our equity incentive plans; or (d) the issuance of 3,636,926 shares of our common stock that is contingent upon satisfaction of a development milestone under our Stock Purchase Agreement dated January 6, 2011 with Intrexon Corporation; and (e) issuances in connection with a strategic partnership, joint venture, collaboration, merger or the acquisition or license of any business products or technology, provided that the shares so issued shall not exceed 5% of the total outstanding shares of the Company immediately following the completion of the offering, and the recipient of such shares agrees to not sell, offer, dispose of or otherwise transfer any such shares without the consent of Barclays Capital Inc. prior to the expiration of the restricted period described above; and

with respect to our officers and directors, (a) the transfer of any or all of the shares of our common stock, either during his or her lifetime or on death, by gift, will or intestate succession to the immediate family of such person or to a trust the beneficiaries of which are exclusively such person and/or a member or members of his or her immediate family or (b) the sale of shares of common stock after March 31, 2011 by a director upon the vesting of shares of restricted common stock outstanding as of the date hereof as necessary to satisfy tax withholding obligations pursuant to our equity compensation plans or arrangements; provided that in the case of (a), it shall be a condition so such transfer that (i) the transferee executes and delivers to Barclays Capital an agreement stating that the transferee is receiving and holding the shares subject to the provisions of the lock-up agreement, and there shall be no further transfer of such shares, except in accordance with the lock-up agreement, (ii) no filing by any transferor or transferee under the Exchange Act shall be required or shall be voluntarily made in connection with such transfer or distribution (other than a filing on a Form 5, Schedule 13D or Schedule 13G (or 13D-A or 13G-A) made after the expiration of the 90-day restricted period referred to above), (iii) each transferor or transferee shall not be required by

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law (including without limitation the disclosure requirements of the Securities Act and the Exchange Act) to make, and shall agree to not voluntarily make, any public announcement of the transfer or disposition, and (iv) the transferor notifies Barclays Capital Inc. at least two business days prior to the proposed transfer or disposition (except with respect to any transfer or disposition of shares of common stock as the result of the death of the transferor), and provided that in the case of (b), such dispositions and sales shall not exceed 40% of the number of shares of restricted common stock so vesting.

Barclays Capital Inc., in its sole discretion, may release the common stock and other securities subject to the lock-up agreements described above in whole or in part at any time with or without notice. When determining whether or not to release the common stock and other securities from lock-up agreements, Barclays Capital Inc. will consider, among other factors, the holder s reasons for requesting the release, the number of shares of common stock or other securities for which the release is being requested and market conditions at the time.

Intrexon Corporation Purchase

Intrexon Corporation, a corporation affiliated with Randal J. Kirk, who serves as a director of the Company agreed to purchase 1,910,000 shares of common stock in this offering.

Indemnification

We have agreed to indemnify the underwriter against certain liabilities, including liabilities under the Securities Act, and to contribute to payments that the underwriter may be required to make for these liabilities.

Listing

Our common stock is listed on The NASDAQ Capital Market under the symbol ZIOP .

Stabilization and Short Positions

The underwriter may engage in stabilizing transactions, covering transactions or purchases for the purpose of pegging, fixing or maintaining the price of the common stock, in accordance with Regulation M under the Exchange Act:

Stabilizing transactions permit bids to purchase the underlying security so long as the stabilizing bids do not exceed a specified maximum.

Covering transactions involve purchases of the common stock in the open market after the distribution has been completed in order to cover short positions.

These stabilizing transactions and covering transactions may have the effect of raising or maintaining the market price of our common stock or preventing or retarding a decline in the market price of the common stock. As a result, the price of the common stock may be higher than the price that might otherwise exist in the open market. These transactions may be effected on the NASDAQ Capital Market or otherwise and, if commenced, may be discontinued at any time.

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

Passive Market Making

In connection with the offering, the underwriter and selling group members may engage in passive market making transactions in the common stock on the NASDAQ Capital Market in accordance with Rule 103 of Regulation M under the Securities Exchange Act of 1934 during the period before the commencement of offers or sales of common stock and extending through the completion of distribution. A passive market maker must display its bids at a price not in excess of the highest independent bid of the security. However, if all independent bids are lowered below the passive market maker s bid that bid must be lowered when specified purchase limits are exceeded.

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Electronic Distribution

A prospectus supplement and the accompanying prospectus in electronic format may be made available on the Internet sites or through other online services maintained by the underwriter or by its affiliates. In those cases, prospective investors may view offering terms online and, depending upon the particular underwriter, prospective investors may be allowed to place orders online. The underwriter may agree with us to allocate a specific number of shares for sale to online brokerage account holders. Any such allocation for online distributions will be made by the underwriter on the same basis as other allocations.

Other than the prospectus supplement and the accompanying prospectus in electronic format, the information on the underwriter s website and any information contained in any other website maintained by the underwriter is not part of the prospectus supplement and the accompanying prospectus or the registration statement of which the prospectus supplement and the accompanying prospectus forms a part, has not been approved and/or endorsed by us or the underwriter in its capacity as underwriter and should not be relied upon by investors.

Stamp Taxes

If you purchase shares of common stock offered in the prospectus, you may be required to pay stamp taxes and other charges under the laws and practices of the country of purchase, in addition to the offering price listed on the cover page of the prospectus.

Relationships

Barclays Capital Inc. and/or and its affiliates may in the future perform investment banking and advisory services for us from time to time for which they expect to receive customary fees and expense reimbursement.

Selling Restrictions

European Economic Area

In relation to each member state of the European Economic Area that has implemented the Prospectus Directive (each, a relevant member state), with effect from and including the date on which the Prospectus Directive is implemented in that relevant member state (the relevant implementation date), an offer of securities described in this prospectus supplement may not be made to the public in that relevant member state other than:

to any legal entity that is authorized or regulated to operate in the financial markets or, if not so authorized or regulated, whose corporate purpose is solely to invest in securities;

to any legal entity that has two or more of (1) an average of at least 250 employees during the last financial year; (2) a total balance sheet of more than €43,000,000 and (3) an annual net turnover of more than €50,000,000, as shown in its last annual or consolidated accounts;

to fewer than 100 natural or legal persons (other than qualified investors as defined in the Prospectus Directive) subject to obtaining the prior consent of Barclays Capital Inc. or its affiliates; or

in any other circumstances that do not require the publication of a prospectus pursuant to Article 3 of the Prospectus Directive,

provided that no such offer of securities shall require us to publish a prospectus pursuant to Article 3 of the Prospectus Directive.

For purposes of this provision, the expression an offer of securities to the public in any relevant member state means the communication in any form and by any means of sufficient information on the terms of the offer and the securities to be offered so as to enable an investor to decide to purchase or subscribe the securities, as the expression may be varied in that member state by any measure implementing the Prospectus Directive in that member state, and the expression Prospectus Directive means Directive 2003/71/EC and includes any relevant implementing measure in each relevant member state.

We have not authorized and do not authorize the making of any offer of securities through any financial intermediary on their behalf, other than offers made by Barclays Capital Inc. or its affiliates with a view to the

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final placement of the securities as contemplated in this prospectus supplement. Accordingly, no purchaser of the securities, other than Barclays Capital Inc. or its affiliates, is authorized to make any further offer of the securities on behalf of us or Barclays Capital Inc. or its affiliates.

United Kingdom

This prospectus supplement is only being distributed to, and is only directed at, persons in the United Kingdom that are qualified investors within the meaning of Article 2(1)(e) of the Prospectus Directive (Qualified Investors) that are also (i) investment professionals falling within Article 19(5) of the Financial Services and Markets Act 2000 (Financial Promotion) Order 2005 (the Order) or (ii) high net worth entities, and other persons to whom it may lawfully be communicated, falling within Article 49(2)(a) to (d) of the Order (all such persons together being referred to as relevant persons). This prospectus supplement and its contents are confidential and should not be distributed, published or reproduced (in whole or in part) or disclosed by recipients to any other persons in the United Kingdom. Any person in the United Kingdom that is not a relevant persons should not act or rely on this document or any of its contents.

Australia

No prospectus supplement or other disclosure document (as defined in the Corporations Act 2001 (Cth) of Australia (Corporations Act)) in relation to the common stock has been or will be lodged with the Australian Securities & Investments Commission (ASIC). This document has not been lodged with ASIC and is only directed to certain categories of exempt persons. Accordingly, if you receive this document in Australia:

(a) you confirm and warrant that you are either:

(i) a sophisticated investor under section 708(8)(a) or (b) of the Corporations Act;

(ii) a sophisticated investor under section 708(8)(c) or (d) of the Corporations Act and that you 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 the offer has been made;

(iii) a person associated with the company under section 708(12) of the Corporations Act; or

(iv) a professional investor within the meaning of section 708(11)(a) or (b) of the Corporations Act, and to the extent that you are unable to confirm or warrant that you are an exempt sophisticated investor, associated person or professional investor under the Corporations Act any offer made to you under this document is void and incapable of acceptance; and

(b) you warrant and agree that you will not offer any of the common stock for resale in Australia within 12 months of those common stock being issued unless any such resale offer is exempt from the requirement to issue a disclosure document under section 708 of the Corporations Act.

Hong Kong

The common stock may not be offered or sold in Hong Kong, by means of any document, other than (a) to professional investors as defined in the Securities and Futures Ordinance (Cap. 571, Laws of Hong Kong) and any rules made under that Ordinance or (b) in other circumstances which do not result in the document being a prospectus

as defined in the Companies Ordinance (Cap. 32, Laws of Hong Kong) or which do not constitute an offer to the public within the meaning of that Ordinance. No advertisement, invitation or document relating to the common stock may be issued or may be in the possession of any person for the purpose of the issue, whether in Hong Kong or elsewhere, which is directed at, or the contents of which are likely to be read by, the public in Hong Kong (except if permitted to do so under the laws of Hong Kong) other than with respect to the common stock which are intended to be disposed of only to persons outside Hong Kong or only to professional investors as defined in the Securities and Futures Ordinance (Cap. 571, Laws of Hong Kong) or any rules made under that Ordinance.

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

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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

No securities registration statement (SRS) has been filed under Article 4, Paragraph 1 of the Financial Instruments and Exchange Law of Japan (Law No. 25 of 1948, as amended) (FIEL) in relation to the common stock. The common stock is being offered in a private placement to qualified institutional investors (tekikaku-kikan-toshika) under Article 10 of the Cabinet Office Ordinance concerning Definitions provided in Article 2 of the FIEL (the Ministry of Finance Ordinance No. 14, as amended) (QIIs), under Article 2, Paragraph 3, Item 2 i of the FIEL. Any QII acquiring the common stock in this offer may not transfer or resell those shares except to other QIIs.

Korea

The common stock 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 common stock has not been registered with the Financial Services Commission of Korea for public offering in Korea. Furthermore, the common stock may not be resold to Korean residents unless the purchaser of the common stock 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 common stock.

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 common stock may not be circulated or distributed, nor may the common stock 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 Future Act, Chapter 289 of Singapore (the SFA), (ii) to a relevant person as defined in Section 275(2) of the SFA, 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 common stock is subscribed and purchased under Section 275 of the SFA by a relevant person which is:

(a) a corporation (which is not an accredited investor (as defined in Section 4A of the SFA)) 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 (as defined in Section 4A of the SFA)) whose sole whole purpose is to hold investments and each beneficiary is an accredited investor,

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shares, debentures and units of shares and debentures of that corporation or the beneficiaries rights and interest (howsoever described) in that trust shall not be transferable within six months after that corporation or that trust has acquired the common stock under Section 275 of the SFA except:

(i) to an institutional investor under Section 274 of the SFA or to a relevant person (as defined in Section 275(2) of the SFA) and in accordance with the conditions, specified in Section 275 of the SFA;

(ii) (in the case of a corporation) where the transfer arises from an offer referred to in Section 275(1A) of the SFA, or (in the case of a trust) where the transfer arises from an offer that is made on terms that such rights or interests are acquired at a consideration of not less than $200,000 (or its equivalent in a foreign currency) for each transaction, whether such amount is to be paid for in cash or by exchange of securities or other assets;

(iii) where no consideration is or will be given for the transfer; or

(iv) where the transfer is by operation of law.

By accepting this prospectus supplement, the recipient hereof represents and warrants that he is entitled to receive it in accordance with the restrictions set forth above and agrees to be bound by limitations contained herein. Any failure to comply with these limitations may constitute a violation of law.

LEGAL MATTERS

Maslon Edelman Borman & Brand, LLP, Minneapolis, Minnesota will pass upon the validity of the issuance of the common stock offered by this prospectus supplement and the accompanying prospectus. The underwriter is being represented by Cooley LLP, Palo Alto, California.

EXPERTS

The balance sheets of ZIOPHARM Oncology, Inc. as of December 31, 2009 and 2008 and the related statements of operations, changes in convertible preferred stock and stockholders equity (deficit) and cash flows for each of the years in the three-year period ended December 31, 2009 and for the period from September 9, 2003 (date of inception) through December 31, 2009, incorporated by reference in this prospectus, have been incorporated by reference herein in reliance on the report, dated March 17, 2010, of Caturano and Company, Inc. (formerly Caturano and Company, P.C.), independent registered public accounting firm, which report expresses an unqualified opinion and includes an explanatory paragraph relating to the change in the manner in which the Company accounts for certain warrants, given on the authority of that firm as experts in auditing and accounting.

WHERE YOU CAN FIND MORE INFORMATION

We have filed with the Securities and Exchange Commission, or the SEC, a registration statement on Form S-3 (No. 333-166444) under the Securities Act relating to the common stock offered by this prospectus supplement and the accompanying prospectus. This prospectus supplement and the accompanying prospectus are a part of that registration statement, which includes additional information not contained in this prospectus supplement or the accompanying prospectus.

We file annual, quarterly and current reports, proxy statements and other information with the SEC. Our SEC filings are available to the public over the Internet at the SEC s website at *http://www.sec.gov*. Copies of certain information filed by us with the SEC are also available on our website at www.ziopharm.com. Our website is not a part of this prospectus supplement. You may also read and copy any document we file with the SEC at its public reference room, at 100 F Street, N.E., Washington, D.C. 20549. Please call the SEC at 1 800 SEC 0330 for further information on the operation of its Public Reference Room.

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INCORPORATION OF CERTAIN INFORMATION BY REFERENCE

We are allowed to incorporate by reference information contained in documents that we file with the SEC. This means that we can disclose important information to you by referring you to those documents and that the information in this prospectus supplement is not complete and you should read the information incorporated by reference for more detail. We incorporate by reference in two ways. First, we list certain documents that we have already filed with the SEC. The information in these documents is considered part of this prospectus supplement. Second, the information in documents that we file in the future will update and supersede the current information in, and incorporated by reference in, this prospectus supplement.

We incorporate by reference the documents listed below and any future filings we will make with the SEC under Section 13(a), 13(c), 14 or 15(d) of the Exchange Act (other than information furnished in Current Reports on Form 8-K filed under Item 2.02 or 7.01 of such form):

our Annual Report on Form 10-K for the fiscal year ended December 31, 2009, filed on March 17, 2010, as amended by Amendment No. 1 to Annual Report on Form 10-K/A filed on April 30, 2010;

our Quarterly Report on Form 10-Q for the quarter ended March 31, 2010, filed on April 30, 2010;

our Quarterly Report on Form 10-Q for the quarter ended June 30, 2010, filed on July 30, 2010;

our Quarterly Report on Form 10-Q for the quarter ended September 30, 2010, filed on November 4, 2010;

our Current Reports on Form 8-K filed on January 27, 2010, April 6, May 21, June 2, June 7, June 21, June 23, July 20, July 30, September 23, September 27, November 12 and December 28, 2010 and January 5, January 12, January 26 and February 2, 2011;

our definitive proxy statement filed pursuant Section 14 of the Exchange Act in connection with our 2010 Annual Meeting of Stockholders filed with the SEC on May 14, 2010; and

The description of our common stock set forth in the registration statement on Form 8-A registering our common stock under Section 12 of the Exchange Act, which was filed with the SEC on September 20, 2006, including any amendments or reports filed for the purpose of updating such description.

We will provide to each person, including any beneficial owner, to whom a prospectus supplement is delivered, a copy of any or all of the information that has been incorporated by reference in this prospectus supplement but not delivered with this prospectus supplement. You may request a copy of this information at no cost, by writing or telephoning us at the following address or telephone number:

ZIOPHARM Oncology, Inc.
1180 Avenue of the Americas, 19th Floor
New York, NY 10036
Attention: President
Telephone: (646) 214-0700

You should rely only on the information incorporated by reference or provided in this prospectus supplement or the accompanying prospectus. We have not authorized anyone else to provide you with different information. You should not assume that the information in this prospectus supplement is accurate as of any date other than the date on the front of this prospectus supplement.

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PROSPECTUS

$100,000,000

ZIOPHARM Oncology, Inc.

Common Stock, Preferred Stock, Warrants and Debt Securities

We may offer and sell any combination of common stock, preferred stock, warrants and debt securities, with a total initial offering price of up to $100,000,000.

This prospectus provides a general description of securities we may offer and sell from time to time. Each time we sell these securities, we will provide their specific terms in a supplement to this prospectus. This prospectus supplement may also add, update or change information contained in this prospectus. You should read this prospectus and the applicable prospectus supplement carefully before you invest in any securities. This prospectus may not be used to consummate a sale of securities unless accompanied by the applicable prospectus supplement.

We may offer and sell these securities, from time to time, to or through one or more underwriters, dealers and agents, or directly to purchasers, on a continuous or delayed basis, at prices and on other terms to be determined at the time of offering. If we use agents, underwriters or dealers to sell the securities, we will name them and describe their compensation in a prospectus supplement.

Our common stock is listed on the Nasdaq Capital Market under the symbol ZIOP. On May 7, 2010, the closing price of our common stock, as reported on the Nasdaq Capital Market, was $5.62. We urge prospective purchasers of our common stock to obtain current information about the market prices of our common stock.

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

The date of this Prospectus is May 10, 2010.

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ZIOPHARM ONCOLOGY, INC.

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ABOUT THIS PROSPECTUS

This prospectus is part of a registration statement that we filed with the Securities and Exchange Commission, or SEC, using a shelf registration process. Under this shelf registration process, from time to time, we may sell any combination of the securities described in this prospectus in one or more offerings, up to a total dollar amount of $100,000,000. This prospectus provides you with a general description of the securities we may offer. Each time we offer and sell securities under this prospectus, we will provide a prospectus supplement that will contain more specific information about the terms of the applicable offering. We may also add, update or change in the prospectus supplement any of the information contained in this prospectus. This prospectus, together with the applicable prospectus supplement(s) and the documents incorporated by reference into this prospectus and such supplement(s), includes all material information relating to this offering. To the extent there is a conflict between the information contained in this prospectus and the prospectus supplement, you should rely on the information in the prospectus supplement; provided that, if any statement in one of these documents is inconsistent with a statement in another document having a later date for example, a document incorporated by reference in this prospectus or any prospectus supplement the statement in the document having the later date modifies or supersedes the earlier statement. Please carefully read both this prospectus and any prospectus supplement, together with the additional information described below under Where You Can Find More Information, before buying securities in this offering.

You should rely only on the information contained or incorporated by reference in this prospectus or a prospectus supplement. We have not authorized any other person to provide you with different information. If anyone provides you with different or inconsistent information, you should not rely on it. This prospectus and the accompanying supplement to this prospectus do not constitute an offer to sell or the solicitation of an offer to buy any securities other than the registered securities to which they relate, nor do this prospectus and the accompanying supplement to this

prospectus constitute an offer to sell or the solicitation of an offer to buy securities in any jurisdiction to any person to whom it is unlawful to make such offer or solicitation in such jurisdiction. You should not assume that the information contained in this prospectus and the accompanying prospectus supplement is accurate on any date subsequent to the date set forth on the front cover of this document or that any information we have incorporated by reference is correct on any date subsequent to the date of the document incorporated by reference, even though this prospectus and any accompanying prospectus supplement is delivered or securities sold on a later date.

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

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PROSPECTUS SUMMARY

The following is a summary of this prospectus. Because it is only a summary, it does not contain all of the detailed information contained elsewhere in this prospectus or in the documents incorporated by reference into this prospectus or included as exhibits to the registration statement that contains this prospectus. Accordingly, you are urged to carefully review this prospectus (including all documents incorporated by reference into this prospectus) in its entirety. Unless otherwise indicated, ZIOPHARM, our Company, we, us, our and similar terms refer to ZIOPHARM Oncology, Inc.

Our Company

ZIOPHARM Oncology, Inc. is a biopharmaceutical company that is seeking to develop and commercialize a diverse, risk-sensitive portfolio of in-licensed cancer drugs that can address unmet medical needs through enhanced efficacy and/or safety and quality of life. Our principal focus is on the licensing and development of proprietary small molecule drug candidates that are related to cancer therapeutics already on the market or in development and that can be administered by intravenous and/or oral capsule dosing. We believe this strategy will result in lower risk and expedited drug development programs with product candidates having a low cost of manufacturing to address changing reimbursement requirements around the world. While we may endeavor to commercialize our products on our own in North America, we recognize that favorable clinical trial results can be better addressed by partnering with companies with the requisite financial resources. With partnering, we could also negotiate the right to complete development and marketing in certain geographies, especially for certain limited (niche) indications. Although we are currently in phase I and/or II studies for three product candidates identified as darinaparsin (Zinapar™, ZIO-101), palifosfamide (Zymafos™, ZIO-201), and indibulin (Zybulin™, ZIO-301), our primary focus has been and remains on palifosfamide development and more specifically on completing the ongoing randomized phase II trial with palifosfamide to support a registration trial for palifosfamide in combination with doxorubicin in the front- and second-line setting of soft tissue sarcoma. We anticipate the initiation of such a registration trial as early as the first half of 2010.

ZIO-101 or darinaparsin (Zinapar™) is an anti-mitochondrial (organic arsenic) compound covered by issued patents and pending patent applications in the U.S. and in foreign countries. A form of commercially available inorganic arsenic (arsenic trioxide [Trisenox®] or ATO) has been approved in the United States and the European Union and Japan for the treatment of acute promyelocytic leukemia, a precancerous condition. In the United States, ATO is on the compendia listing for the therapy of multiple myeloma, and has been studied for the treatment of various other cancers. Nevertheless, ATO has been shown to be toxic to the heart, liver, and brain, which limits its use as an anti-cancer agent. ATO carries a black box warning for ECG abnormalities since arsenic trioxide has been shown to cause QT interval prolongation and complete atrioventricular block. QT prolongation can lead to a torsade de pointes-type ventricular arrhythmia, which can be fatal. Inorganic arsenic has also been shown to cause cancer of the skin and lung in humans. The toxicity of arsenic is generally correlated to its accumulation in organs and tissues. Our preclinical and clinical studies to date have demonstrated that darinaparsin is considerably less toxic than ATO, particularly with regard to cardiac toxicity. In vitro testing of darinaparsin using the National Cancer Institute s human cancer cell panel demonstrated activity against a series of tumor cell lines including lung, colon, brain, melanoma, ovarian, and kidney cancer. Moderate activity was shown against breast and prostate cancer tumor cell lines. In addition to solid tumors, in vitro testing in both the National Cancer Institute s cancer cell panel and in vivo testing in a leukemia animal model demonstrated substantial activity against hematological cancers (cancers of the blood and blood-forming tissues) such as leukemia, lymphoma, myelodysplastic syndromes, and multiple myeloma. Results indicate significant activity against the HuT 78 cutaneous T-cell lymphoma, the NK-G2MI natural killer-cell NHL,

KARPAS-299 T-cell NHL, SU-DHL-8 B-cell NHL, SU-DHL-10 B-cell NHL and SU-DHL-16 B-cell NHL cell lines. Preclinical studies have also established anti-angiogenic properties of darinaparsin and provided support for the development of an oral capsule form of the drug, and established synergy of darinaparsin in combination with other approved anti-cancer agents.

Phase I testing of the intravenous (IV) form of darinaparsin in solid tumors and hematological cancers has been completed. We reported clinical activity and, importantly, a safety profile from these studies as

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predicted by preclinical results. We subsequently completed Phase II studies in advanced myeloma and primary liver cancer and are nearing completion of a Phase II study in certain other hematological cancers. In addition, we are completing two Phase I studies with an oral capsule form of darinaparsin. At the May 2009 annual meeting of the American Society of Clinical Oncology, we reported favorable results from the trial with IV-administered darinaparsin in lymphoma, particularly peripheral T-cell lymphoma. In the ongoing Phase I trials, also reported at the ASCO annual meeting, preliminary data primarily in solid tumors indicate the oral form is active and well tolerated. We are completing data collection from the IV Phase II trial to address a registration and other trials with the U.S. Food and Drug Administration. The oral Phase I program will be progressed to establish a dose for further clinical testing.

ZIO-201 or palifosfamide (Zymafos™), comprises the active metabolite of ifosfamide, a compound chemically related to cyclophosphamide. Patent applications covering proprietary forms of palifosfamide for pharmaceutical composition and method of use have been filed in the U.S. and internationally and in the U.S. we recently received a patent covering pharmaceutical composition. Like cyclophosphamide, ifosfamide and bendamustine, palifosfamide is a DNA alkylating agent, a form of cancer therapy to treat a wide range of solid tumors and hematological malignancies. We believe that cyclophosphamide is the most widely used alkylating agent in cancer therapy, with significant use in the treatment of breast cancer and non-Hodgkin s lymphoma. Bendamustine has been recently approved and successfully launched by Cephalon Oncology in the U.S. and Europe to treat certain hematological malignancies. Ifosfamide has been shown to be effective in the treatment of sarcoma and lymphoma, either by itself or in combination with other anticancer agents. Ifosfamide is approved by the FDA as a treatment for testicular cancer while ifosfamide-based treatment is a standard of care for sarcoma, although it is not licensed for this indication by the FDA. Preclinical studies have shown that palifosfamide has activity against leukemia and solid tumors. These studies also indicate that palifosfamide may have a better safety profile than ifosfamide or cyclophosphamide because it does not appear to produce known toxic metabolites of ifosfamide, such as acrolein and chloroacetaldehyde. Acrolein, which is toxic to the kidneys and bladder, can mandate the administration of a protective agent called mesna, which is inconvenient and expensive. Chloroacetaldehyde is toxic to the central nervous system, causing fuzzy brain syndrome for which there is currently no protective measure. Similar toxicity concerns pertain to high-dose cyclophosphamide, which is widely used in bone marrow and blood cell transplantation. Palifosfamide has evidenced activity against ifosfamide- and/or cyclophosphamide-resistant cancer cell lines. Also in preclinical cancer models, palifosfamide was shown to be orally active and encouraging results have been obtained with palifosfamide in combination with doxorubicin, an agent approved to treat sarcoma.

Following completion of Phase I study, we completed Phase II testing of the intravenous form of palifosfamide as a single agent to treat advanced sarcoma. In both Phase I and Phase II testing, palifosfamide has been administered without the uroprotectant mesna, and the toxicities associated with acrolein and chloroacetaldehyde have not been observed. We reported clinical activity of palifosfamide when used alone in the Phase II study addressing advanced sarcoma. Following review of preclinical combination studies, clinical data, and discussion with sarcoma experts, we initiated a Phase I dose escalation study of palifosfamide in combination with doxorubicin primarily in patients with soft tissue sarcoma. We reported favorable results and safety profile from this study at ASCO s 2009 annual meeting.

In light of reported favorable Phase II clinical activity data and with the combination of palifosfamide with doxorubicin well tolerated in the Phase I trial and evidencing activity, we initiated a Phase II randomized controlled trial in the second half of 2008 to compare doxorubicin plus palifosfamide to doxorubicin alone in patients with front and second-line metastatic or unresectable soft tissue sarcoma. The study has generated positive top line interim data in 2009. Upon reaching a pre-specified efficacy milestone and following safety and efficacy data review by the Data Committee, sarcoma experts, and our Medical Advisory Board, we elected to suspend enrollment in the trial in October 2009. We subsequently presented further positive interim data from the trial at the 15th Annual Connective Tissue Oncology Society meeting held in November 2009. We currently plan to initiate a registration trial following regulatory review of the palifosfamide program to date. We are also developing an oral capsule form of palifosfamide to be studied clinically following receipt of further data from the IV trials and subject to obtaining sufficient additional

sources of funding, either from potential

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partnering arrangements or from other sources. To date we have no such partnering arrangements or other sources of such financing in place. We are also considering additional Phase II trials in other solid tumors as funding becomes available. Orphan Drug Designation for palifosfamide has been obtained in both the United States and the European Union for the treatment of soft tissue sarcomas.

ZIO-301 or indibulin (Zybulin™), is a novel, orally available small molecular-weight inhibitor of tubulin polymerization that we acquired from Baxter Healthcare in 2006 and is the subject of numerous patents worldwide, including the United States, the European Union and Japan. The microtubule component, tubulin, is one of the more well established drug targets in cancer. Microtubule inhibitors interfere with the dynamics of tubulin polymerization, resulting in inhibition of chromosome segregation during mitosis and consequently inhibition of cell division. A number of marketed IV anticancer drugs target tubulin, such as the taxane family members, paclitaxel (Taxol®), docetaxel (Taxotere®), the Vinca alkaloid family members, vincristine and vinorelbine, and the new class of epothilones with Ixempra™ marketed. This class of agents is typically the mainstay of therapy in a wide variety of indications. In spite of their effectiveness, the use of these drugs is associated with significant toxicities, notably peripheral neurotoxicity.

Preclinical studies with indibulin demonstrate significant and broad antitumor activity, including activity against taxane-refractory cell lines. The cytotoxic activity of indibulin was demonstrated in several rodent and human tumor cell lines derived from prostate, brain, breast, pancreas, lung, ovary, and cervical tumor tissues and in rodent tumor and human tumor xenograft models. In addition, indibulin was effective against multidrug resistant tumor cell lines (breast, lung, and leukemia) both in vitro and in vivo. Indibulin is potentially safer than other tubulin inhibitors. No neurotoxicity has been observed at therapeutic doses in rodents and in the Phase I trials. Indibulin has also demonstrated synergy with approved anti-cancer agents in preclinical studies. The availability of an oral capsule formulation of indibulin creates significant commercial opportunity because no oral capsule formulations of the taxane family are currently on the market in the United States.

Indibulin, as a single agent, has completed Phase I trials in patients with advanced solid tumors. We have reported clinical activity at well-tolerated doses using a continuous dosing scheme without the development of clinically relevant peripheral neuropathy. Following encouraging results obtained with indibulin in combination with erlotinib, and 5-FU in preclinical models, two Phase I combination studies were initiated with Tarceva™ and Xeloda™, respectively. Favorable activity and safety profile of oral indibulin with oral Xeloda™ were reported at ASCO s annual meeting in May 2009. Preclinical work with our consultant, Dr. Larry Norton, to explore dose scheduling for the clinical setting have been completed, with results supporting the recently initiated Phase I safety trial necessary for a Phase I/II breast cancer trial and using the mathematical dose schedule / frequency established preclinically.

We intend to continue with clinical development of IV palifosfamide for soft tissue sarcoma both completing the ongoing **P**hase II multicenter, parallel group, randomized study of pal**I**fosfamide tris plus doxorubicin versus doxorubi**C**in in subjects with unresect**A**ble or metastatic **S**oft tissue **S**arc**O**ma (PICASSO) trial and in a planned registration trial and, with additional resources, to initiate a clinical study with the oral form and/or in additional indications beyond STS. For IV darinaparsin, we will complete the ongoing Phase I oral trial and will address peripheral T-cell lymphoma (PTCL) registration and other trials, in part dependent on additional funding. For oral indibulin, we will complete the Phase I breast cancer safety trial and initiate the subsequent Phase I/II trial and, with additional funding, other trials. However, the successful development of our product candidates is highly uncertain. Product development costs and timelines can vary significantly for each product candidate, are difficult to accurately predict, and will require us to obtain additional funding, either alone or in connection with partnering arrangements. Various statutes and regulations also govern or influence the manufacturing, safety, labeling, storage, record keeping and marketing of each product. The lengthy process of seeking approval and the subsequent compliance with applicable statutes and regulations require the expenditure of substantial resources. Any failure by us to obtain, or any delay in obtaining, regulatory approvals could materially, adversely affect our business. To date, we have not received

approval for the sale of any drug candidates in any market and, therefore, have not generated any revenues from our drug candidates.

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Corporate Information

We were originally incorporated in Colorado in September 1998 (under the name Net Escapes, Inc.) and later changed our name to EasyWeb, Inc. in February 1999. We were re-incorporated in Delaware on May 16, 2005 under the same name. On September 13, 2005, we completed a reverse acquisition of privately held ZIOPHARM, Inc., a Delaware corporation. To effect this transaction, we caused ZIO Acquisition Corp., our wholly-owned subsidiary, to merge with and into ZIOPHARM, Inc., with ZIOPHARM, Inc. surviving as our wholly owned subsidiary. In accordance with the terms of the merger, the outstanding common stock of ZIOPHARM, Inc. automatically converted into the right to receive an aggregate of approximately 97.3% of our outstanding common stock (after giving effect to the transaction). Following the merger, we caused ZIOPHARM, Inc. to merge with and into us and we changed our name to ZIOPHARM Oncology, Inc. Although EasyWeb, Inc. was the legal acquirer in the transaction, we accounted for the transaction as a reverse acquisition under generally accepted accounting principles. As a result, ZIOPHARM, Inc. became the registrant with the Securities and Exchange Commission and the historical financial statements of ZIOPHARM, Inc. became our historical financial statements.

Our executive offices are located at 1180 Avenue of the Americas, 19th Floor, New York, NY 10036, and our telephone number is (646) 214-0700. Our internet site is *www.ziopharm.com*. None of the information on our internet site is part of this prospectus.

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RISK FACTORS

As with most pharmaceutical product candidates, the development of our product candidates is subject to numerous risks, including the risk of delays in or discontinuation of development from lack of financing, inability to obtain necessary regulatory approvals to market the products, unforeseen safety issues relating to the products and dependence on third party collaborators to conduct research and development of the products. Because we are a development stage company with a limited history of operations, we are also subject to many risks associated with early-stage companies. For a more detailed discussion of the risks you should consider before purchasing shares of our common stock, you should carefully consider the specific risks discussed under Risk Factors in the applicable prospectus supplement and in our filings with the Securities and Exchange Commission that are incorporated by reference in this prospectus and such prospectus supplement.

SPECIAL NOTE REGARDING FORWARD-LOOKING STATEMENTS

This prospectus contains, and the documents incorporated by reference herein and in any prospectus supplement hereto may contain, forward-looking statements within the meaning of Section 27A of the Securities Act of 1933, as amended (the Securities Act), and Section 21E of the Securities Exchange Act of 1934, as amended (the Exchange Act). These statements relate to future events or to our future financial performance and involve known and unknown risks, uncertainties and other factors which may cause our actual results, performance or achievements to be materially different from any future results, performances or achievements expressed or implied by the forward-looking statements. Forward-looking statements may include, but are not limited to statements about:

the progress and timing of preclinical and clinical trials involving our drug candidates;
the progress and timing of our research and development programs;
the benefits to be derived from relationships with our collaborators;
the receipt or anticipated receipt of regulatory clearances and approvals;
our ability to enforce intellectual property rights;
our estimates of future revenues and profitability; and
our estimates regarding our capital requirements and our need for additional financing.

In some cases, you can identify forward-looking statements by terms such as may, will, should, could, would, plans, anticipates, believes, estimates, projects, predicts, potential and similar expressions intended to forward-looking statements. These statements reflect our current views with respect to future events and are based on assumptions and subject to risks and uncertainties. Given these uncertainties, you should not place undue reliance on these forward-looking statements. We discuss many of these risks in greater detail under the heading Risk Factors in the applicable prospectus supplement and in our reports filed from time to time under the Securities Act and/or the Exchange Act. We encourage you to read these filings as they are made.

Further, any forward-looking statement speaks only as of the date on which it is made, and we undertake no obligation to update any forward-looking statement or statements to reflect events or circumstances after the date on which such statement is made or to reflect the occurrence of unanticipated events. New factors emerge from time to time, and it is not possible for us to predict which factors will arise. In addition, we cannot assess the impact of each factor on our business or the extent to which any factor, or combination of factors, may cause actual results to differ materially from those contained in any forward-looking statements.

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RATIO OF EARNINGS TO FIXED CHARGES

The following table shows our ratio of earnings to fixed charges for the periods indicated.

	Fiscal Year Ended December 31,					Three Months Ended March 31,
$ In Thousands, Except Ratio	2005	2006	2007	2008	2009	2010
Ratio of earnings to fixed charges[1]						
Deficiency of earnings to fixed charges[2]	$(9,517)	$(17,857)	$(26,608)	$(25,231)	$(7,649)	$(17,653)

(1) In each of the periods presented, no earnings were sufficient to cover fixed charges.

(2) The deficiency of earnings is equivalent to net income (loss) before tax benefit (provision) and extraordinary gain.

USE OF PROCEEDS

We will retain broad discretion over the use of the net proceeds to us from the sale of our securities offered by this prospectus. Unless we indicate otherwise in the applicable prospectus supplement, we anticipate that any net proceeds will be used for working capital and general corporate purposes. We will set forth in the applicable prospectus supplement our intended use for the net proceeds received from the sale of securities sold pursuant to that prospectus supplement.

PLAN OF DISTRIBUTION

We may sell the securities covered by this prospectus:

to or through one or more underwriters or dealers;
directly to purchasers, or to purchasers through agents; or
through a combination of any of these methods of sale.

We may distribute the securities offered hereby:

from time to time in one or more transactions at a fixed price or prices, which may be changed from time to time;
at market prices prevailing at the times of sale;
at prices related to such prevailing market prices; or
at negotiated prices.

We will describe the method of distribution of the securities in the applicable prospectus supplement.

We may determine the price or other terms of the securities offered under this prospectus by use of an electronic auction. We will describe how any auction will determine the price or any other terms, how potential investors may participate in the auction and the nature of the obligations of the underwriter, dealer or agent in the applicable prospectus supplement.

Underwriters, dealers or agents may receive compensation in the form of discounts, concessions or commissions from us or our purchasers (as their agents in connection with the sale of the securities). In addition, underwriters may sell securities to or through dealers, and those dealers may receive compensation in the form of discounts, concessions or commissions from the underwriters and/or commissions from the purchasers for whom they act as agent. These underwriters, dealers or agents may be considered to be underwriters under the Securities Act. As a result, discounts, commissions, or profits on resale received by the underwriters, dealers or agents may be treated as underwriting discounts and commissions. Each applicable prospectus supplement will identify any such underwriter, dealer or agent, and describe any compensation received by them from us. Any initial public offering price and any discounts or concessions allowed or re-allowed or paid to dealers may be changed from time to time.

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We may enter into agreements that provide for indemnification against certain civil liabilities, including liabilities under the Securities Act, or for contribution with respect to payments made by the underwriters, dealers or agents and to reimburse these persons for certain expenses.

We may grant underwriters who participate in the distribution of the securities an option to purchase additional securities to cover over-allotments, if any, in connection with the distribution. Underwriters or agents and their associates may be customers of, engage in transactions with, or perform services for us in the ordinary course of business.

In connection with the offering of the securities, certain underwriters and selling group members and their respective affiliates, may engage in transactions that stabilize, maintain or otherwise affect the market price of the securities. These transactions may include stabilization transactions effected in accordance with Rule 104 of Regulation M promulgated by the SEC pursuant to which these persons may bid for or purchase securities for the purpose of stabilizing its market price.

The underwriters in the offering may engage in overallotment, stabilizing transactions, short covering transactions and penalty bids in accordance with rules and regulations under the Securities Exchange Act of 1934, as amended (the Exchange Act). Overallotment involves sales in excess of the offering size, which create a short position. Stabilizing transactions permit bids to purchase the underlying security so long as the stabilizing bids do not exceed a specified maximum. Short covering transactions involve purchases of the securities in the open market after the distribution is completed to cover short positions. Penalty bids permit the underwriters to reclaim a selling concession from a dealer when the securities originally sold by the dealer are purchased in a covering transaction to cover short positions. Those activities may cause the price of the securities to be higher than it would otherwise be. If commenced, the underwriters may discontinue any of these activities at any time.

In compliance with guidelines of the Financial Industry Regulatory Authority, or FINRA, the maximum consideration or discount to be received by any FINRA member or independent broker dealer may not exceed 8% of the aggregate amount of the securities offered pursuant to this prospectus and any applicable prospectus supplement.

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DESCRIPTION OF CAPITAL STOCK

Pursuant to our certificate of incorporation, as amended and restated to date, our authorized capital stock consists of 280,000,000 shares, comprised of 250,000,000 shares of common stock, par value $.001 per share, and 30,000,000 shares of preferred stock, par value $.001 per share. As of May 7, 2010, there were 41,824,732 shares of common stock and no shares of preferred stock issued and outstanding. Our common stock is traded on the Nasdaq Capital Market under the symbol ZIOP .

The following description summarizes the material terms of our capital stock. This summary is, however, subject to the provisions of our certificate of incorporation and bylaws. For greater detail about our capital stock, please refer to our certificate of incorporation and bylaws.

Common Stock

Voting. The holders of our common stock are entitled to one vote for each outstanding share of common stock owned by such stockholder on every matter properly submitted to the stockholders for their vote. Stockholders are not entitled to vote cumulatively for the election of directors. At any meeting of the stockholders, a quorum as to any matter shall consist of a majority of the votes entitled to be cast on the matter, except where a larger quorum is required by law, by our certificate of incorporation or by our bylaws.

Dividend Rights. Holders of our common stock are entitled to receive ratably dividends and other distributions of cash or any other right or property as may be declared by the registrant s Board of Directors out of our assets or funds legally available for such dividends or distributions. The dividend rights of holders of common stock are subject to the dividend rights of the holders of any series of preferred stock that may be issued and outstanding from time to time.

Liquidation Rights. In the event of any voluntary or involuntary liquidation, dissolution or winding up of our affairs, holders of our common stock would be entitled to share ratably in our assets that are legally available for distribution to stockholders after payment of liabilities. If we have any preferred stock outstanding at such time, the holders of such preferred stock may be entitled to distribution and/or liquidation preferences that require us to pay the applicable distribution to the holders of preferred stock before paying distributions to the holders of common stock.

Conversion, Redemption and Preemptive Rights. Holders of our common stock have no conversion, redemption, preemptive, subscription or similar rights.

The transfer agent and registrar for our common stock is American Stock Transfer and Trust Company.

See Certain Provisions of Delaware Law, the Company s Certificate of Incorporation and Bylaws for a description of provisions of the Company s certificate of incorporation and bylaws which may have the effect of delaying, deferring or preventing changes in the Company s control.

Preferred Stock

The following description of preferred stock and the description of the terms of any particular series of preferred stock that we choose to issue hereunder and that will be set forth in the related prospectus supplement are not complete. These descriptions are qualified in their entirety by reference to the certificate of designation relating to that series. The rights, preferences, privileges and restrictions of the preferred stock of each series will be fixed by the certificate

of designation relating to that series.

The board of directors has the authority, without stockholder approval, subject to limitations prescribed by law, to provide for the issuance of the shares of preferred stock in one or more series, and by filing a certificate pursuant to the applicable law of the State of Delaware, to establish from time to time the number of shares to be included in each such series, and to fix the designation, powers, preferences and rights of the shares of each series and the qualifications, limitations or restrictions, including, but not limited to, the following:

the number of shares constituting that series;
dividend rights and rates;
voting rights;

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conversion terms;
rights and terms of redemption (including sinking fund provisions); and
rights of the series in the event of liquidation, dissolution or winding up.

All shares of preferred stock offered hereby will, when issued, be fully paid and nonassessable and will not have any preemptive or similar rights. Our board of directors could authorize the issuance of shares of preferred stock with terms and conditions that could have the effect of discouraging a takeover or other transaction that might involve a premium price for holders of the shares or which holders might believe to be in their best interests.

We will set forth in a prospectus supplement relating to the series of preferred stock being offered the following items:

the title and stated value of the preferred stock;
the number of shares of the preferred stock offered, the liquidation preference per share and the offering price of the preferred stock;
the dividend rate(s), period(s) and/or payment date(s) or method(s) of calculation applicable to the preferred stock;
whether dividends are cumulative or non-cumulative and, if cumulative, the date from which dividends on the preferred stock will accumulate;
the procedures for any auction and remarketing, if any, for the preferred stock;
the provisions for a sinking fund, if any, for the preferred stock;
the provision for redemption, if applicable, of the preferred stock;
any listing of the preferred stock on any securities exchange;
the terms and conditions, if applicable, upon which the preferred stock will be convertible into common stock, including the conversion price (or manner of calculation) and conversion period;
voting rights, if any, of the preferred stock;
a discussion of any material and/or special United States federal income tax considerations applicable to the preferred stock;
the relative ranking and preferences of the preferred stock as to dividend rights and rights upon the liquidation, dissolution or winding up of our affairs;
any limitations on issuance of any class or series of preferred stock ranking senior to or on a parity with the class or series of preferred stock as to dividend rights and rights upon liquidation, dissolution or winding up of our affairs; and
any other specific terms, preferences, rights, limitations or restrictions of the preferred stock.

The transfer agent and registrar for any series of preferred stock will be set forth in the applicable prospectus supplement.

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DESCRIPTION OF DEBT SECURITIES

General

The terms of each series of debt securities will be established by or pursuant to a resolution of our board of directors and set forth or determined in the manner provided in an officers certificate or by a supplemental indenture. Debt securities may be issued in separate series without limitation as to aggregate principal amount. We may specify a maximum aggregate principal amount for the debt securities of any series. The particular terms of each series of debt securities will be described in a prospectus supplement relating to such series, including any pricing supplement. The prospectus supplement will set forth specific terms relating to some or all of the following:

the offering price;
the title;
any limit on the aggregate principal amount;
the person who shall be entitled to receive interest, if other than the record holder on the record date;
the date the principal will be payable;
the interest rate, if any, the date interest will accrue, the interest payment dates and the regular record dates;
the place where payments may be made;
any mandatory or optional redemption provisions;
if applicable, the method for determining how the principal, premium, if any, or interest will be calculated by reference to an index or formula;
if other than U.S. currency, the currency or currency units in which principal, premium, if any, or interest will be payable and whether we or the holder may elect payment to be made in a different currency;
the portion of the principal amount that will be payable upon acceleration of stated maturity, if other than the entire principal amount;
any defeasance provisions if different from those described below under Satisfaction and Discharge; Defeasance ;
any conversion or exchange provisions;
any obligation to redeem or purchase the debt securities pursuant to a sinking fund;
whether the debt securities will be issuable in the form of a global security;
any subordination provisions, if different from those described below under Subordination ;
any deletions of, or changes or additions to, the events of default or covenants; and
any other specific terms of such debt securities.

Unless otherwise specified in the prospectus supplement, the debt securities will be registered debt securities. Debt securities may be sold at a substantial discount below their stated principal amount, bearing no interest or interest at a rate which at the time of issuance is below market rates.

Exchange and Transfer

Debt securities may be transferred or exchanged at the office of the security registrar or at the office of any transfer agent designated by us.

We will not impose a service charge for any transfer or exchange, but we may require holders to pay any tax or other governmental charges associated with any transfer or exchange.

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In the event of any potential redemption of debt securities of any series, we will not be required to:

issue, register the transfer of, or exchange, any debt security of that series during a period beginning at the opening of business 15 days before the day of mailing of a notice of redemption and ending at the close of business on the day of the mailing; or

register the transfer of or exchange any debt security of that series selected for redemption, in whole or in part, except the unredeemed portion being redeemed in part.

We may initially appoint the trustee as the security registrar. Any transfer agent, in addition to the security registrar, initially designated by us will be named in the prospectus supplement. We may designate additional transfer agents or change transfer agents or change the office of the transfer agent. However, we will be required to maintain a transfer agent in each place of payment for the debt securities of each series.

Global Securities

The debt securities of any series may be represented, in whole or in part, by one or more global securities. Each global security will:

be registered in the name of a depositary that we will identify in a prospectus supplement;

be deposited with the depositary or nominee or custodian; and

bear any required legends.

No global security may be exchanged in whole or in part for debt securities registered in the name of any person other than the depositary or any nominee unless:

the depositary has notified us that it is unwilling or unable to continue as depositary or has ceased to be qualified to act as depositary;

an event of default is continuing; or

the Company executes and delivers to the trustee an officers certificate stating that the global security is exchangeable.

As long as the depositary, or its nominee, is the registered owner of a global security, the depositary or nominee will be considered the sole owner and holder of the debt securities represented by the global security for all purposes under the indenture. Except in the above limited circumstances, owners of beneficial interests in a global security:

will not be entitled to have the debt securities registered in their names;

will not be entitled to physical delivery of certificated debt securities; and

will not be considered to be holders of those debt securities under the indentures.

Payments on a global security will be made to the depositary or its nominee as the holder of the global security. Some jurisdictions have laws that require that certain purchasers of securities take physical delivery of such securities in definitive form. These laws may impair the ability to transfer beneficial interests in a global security.

Institutions that have accounts with the depositary or its nominee are referred to as participants. Ownership of beneficial interests in a global security will be limited to participants and to persons that may hold beneficial interests through participants. The depositary will credit, on its book-entry registration and transfer system, the respective principal amounts of debt securities represented by the global security to the accounts of its participants.

Ownership of beneficial interests in a global security will be shown on and effected through records maintained by the depositary, with respect to participants interests, or any participant, with respect to interests of persons held by participants on their behalf.

Payments, transfers and exchanges relating to beneficial interests in a global security will be subject to policies and procedures of the depositary.

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The depositary policies and procedures may change from time to time. Neither we nor the trustee will have any responsibility or liability for the depositary s or any participant s records with respect to beneficial interests in a global security.

Payment and Paying Agent

The provisions of this paragraph will apply to the debt securities unless otherwise indicated in the prospectus supplement. Payment of interest on a debt security on any interest payment date will be made to the person in whose name the debt security is registered at the close of business on the regular record date. Payment on debt securities of a particular series will be payable at the office of a paying agent or paying agents designated by us. However, at our option, we may pay interest by mailing a check to the record holder. The corporate trust office will be designated as our sole paying agent.

We may also name any other paying agents in the prospectus supplement. We may designate additional paying agents, change paying agents or change the office of any paying agent. However, we will be required to maintain a paying agent in each place of payment for the debt securities of a particular series.

All moneys paid by us to a paying agent for payment on any debt security which remain unclaimed at the end of two years after such payment was due will be repaid to us. Thereafter, the holder may look only to us for such payment.

Consolidation, Merger and Sale of Assets

Except as otherwise set forth in the prospectus supplement, we may not consolidate with or merge into any other person, in a transaction in which we are not the surviving corporation, or convey, transfer or lease our properties and assets substantially as an entirety to, any person, unless:

the successor, if any, is a U.S. corporation, limited liability company, partnership, trust or other entity;
the successor assumes our obligations on the debt securities and under the indenture;
immediately after giving effect to the transaction, no default or event of default shall have occurred and be continuing; and
certain other conditions are met.

Events of Default

Unless we inform you otherwise in the prospectus supplement, the indenture will define an event of default with respect to any series of debt securities as one or more of the following events:

(1) failure to pay principal of or any premium on any debt security of that series when due;
(2) failure to pay any interest on any debt security of that series for 30 days when due;
(3) failure to deposit any sinking fund payment when due;
(4) failure to perform any other covenant in the indenture continued for 90 days after being given the notice required in the indenture;
(5) our bankruptcy, insolvency or reorganization; and
(6) any other event of default specified in the prospectus supplement.

An event of default of one series of debt securities is not necessarily an event of default for any other series of debt securities.

If an event of default, other than an event of default described in clause (5) above, shall occur and be continuing, either the trustee or the holders of at least 25% in aggregate principal amount of the outstanding securities of that series may declare the principal amount of the debt securities of that series to be due and payable immediately.

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If an event of default described in clause (5) above shall occur, the principal amount of all the debt securities of that series will automatically become immediately due and payable. Any payment by us on subordinated debt securities following any such acceleration will be subject to the subordination provisions described below under Subordinated Debt Securities.

After acceleration the holders of a majority in aggregate principal amount of the outstanding securities of that series may, under certain circumstances, rescind and annul such acceleration if all events of default, other than the non-payment of accelerated principal, or other specified amount, have been cured or waived.

Other than the duty to act with the required care during an event of default, the trustee will not be obligated to exercise any of its rights or powers at the request of the holders unless the holders shall have offered to the trustee reasonable indemnity. Generally, the holders of a majority in aggregate principal amount of the outstanding debt securities of any series will have the right to direct the time, method and place of conducting any proceeding for any remedy available to the trustee or exercising any trust or power conferred on the trustee.

A holder will not have any right to institute any proceeding under the indentures, or for the appointment of a receiver or a trustee, or for any other remedy under the indentures, unless:

(1) the holder has previously given to the trustee written notice of a continuing event of default with respect to the debt securities of that series;

(2) the holders of at least 25% in aggregate principal amount of the outstanding debt securities of that series have made a written request and have offered reasonable indemnity to the trustee to institute the proceeding; and

(3) the trustee has failed to institute the proceeding and has not received direction inconsistent with the original request from the holders of a majority in aggregate principal amount of the outstanding debt securities of that series within 90 days after the original request.

Holders may, however, sue to enforce the payment of principal or interest on any debt security on or after the due date without following the procedures listed in (1) through (3) above.

Modification and Waiver

Except as provided in the next two succeeding paragraphs, the applicable trustee and we may make modifications and amendments to the indentures (including, without limitation, through consents obtained in connection with a tender offer or exchange offer for, outstanding securities) and may waive any existing default or event of default (including, without limitation, through consents obtained in connection with a tender offer or exchange offer for, outstanding securities) with the consent of the holders of a majority in aggregate principal amount of the outstanding securities of each series affected by the modification or amendment.

However, neither we nor the trustee may make any amendment or waiver without the consent of the holder of each outstanding security of that series affected by the amendment or waiver if such amendment or waiver would, among other things:

change the amount of securities whose holders must consent to an amendment, supplement or waiver;

change the stated maturity of any debt security;

reduce the principal on any debt security or reduce the amount of, or postpone the date fixed for, the payment of any sinking fund;

reduce the principal of an original issue discount security on acceleration of maturity;

reduce the rate of interest or extend the time for payment of interest on any debt security;

make a principal or interest payment on any debt security in any currency other than that stated in the debt security;

impair the right to enforce any payment after the stated maturity or redemption date;

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waive any default or event of default in payment of the principal of, premium or interest on any debt security (except certain rescissions of acceleration); or

waive a redemption payment or modify any of the redemption provisions of any debt security.

Notwithstanding the preceding, without the consent of any holder of outstanding securities, we and the trustee may amend or supplement the indentures:

to provide for the issuance of and establish the form and terms and conditions of debt securities of any series as permitted by the indenture;

to provide for uncertificated securities in addition to or in place of certificated securities;

to provide for the assumption of our obligations to holders of any debt security in the case of a merger, consolidation, transfer or sale of all or substantially all of our assets;

to make any change that does not adversely affect the legal rights under the indenture of any such holder;

to comply with requirements of the Commission in order to effect or maintain the qualification of an indenture under the Trust Indenture Act; or

to evidence and provide for the acceptance of appointment by a successor trustee with respect to the debt securities of one or more series and to add to or change any of the provisions of the indenture as shall be necessary to provide for or facilitate the administration of the trusts by more than one Trustee.

The consent of holders is not necessary under the indentures to approve the particular form of any proposed amendment. It is sufficient if such consent approves the substance of the proposed amendment.

Satisfaction and Discharge; Defeasance

We may be discharged from our obligations on the debt securities of any series that have matured or will mature or be redeemed within one year if we deposit with the trustee enough cash to pay all the principal, interest and any premium due to the stated maturity date or redemption date of the debt securities.

Each indenture contains a provision that permits us to elect:

to be discharged from all of our obligations, subject to limited exceptions, with respect to any series of debt securities then outstanding; and/or

to be released from our obligations under the following covenants and from the consequences of an event of default resulting from a breach of certain covenants, including covenants as to payment of taxes and maintenance of corporate existence.

To make either of the above elections, we must deposit in trust with the trustee enough money to pay in full the principal and interest on the debt securities. This amount may be made in cash and/or U.S. government obligations. As a condition to either of the above elections, we must deliver to the trustee an opinion of counsel that the holders of the debt securities will not recognize income, gain or loss for federal income tax purposes as a result of the action.

If any of the above events occurs, the holders of the debt securities of the series will not be entitled to the benefits of the indenture, except for the rights of holders to receive payments on debt securities or the registration of transfer and exchange of debt securities and replacement of lost, stolen or mutilated debt securities.

Notices

Notices to holders will be given by mail to the addresses of the holders in the security register.

Governing Law

The indentures and the debt securities will be governed by, and construed under, the law of the State of New York.

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Regarding the Trustee

The indenture limits the right of the trustee, should it become a creditor of us, to obtain payment of claims or secure its claims.

The trustee is permitted to engage in certain other transactions. However, if the trustee acquires any conflicting interest, and there is a default under the debt securities of any series for which they are trustee, the trustee must eliminate the conflict or resign.

Subordination

Payment on subordinated debt securities will, except as otherwise provided in the indenture, be subordinated in right of payment to the prior payment in full of all of our senior indebtedness (except that holders of the notes may receive and retain (i) permitted junior securities and (ii) payments made from the trust described under Satisfaction and Discharge; Defeasance). Any subordinated debt securities also are effectively subordinated to all debt and other liabilities, including lease obligations, if any.

Upon any distribution of our assets upon any dissolution, winding up, liquidation or reorganization, the payment of the principal of and interest on subordinated debt securities will be subordinated in right of payment to the prior payment in full in cash or other payment satisfactory to the holders of senior indebtedness. In the event of any acceleration of subordinated debt securities because of an event of default, the holders of any senior indebtedness would be entitled to payment in full in cash or other payment satisfactory to such holders of all senior indebtedness obligations before the holders of subordinated debt securities are entitled to receive any payment or distribution, except for certain payments made by the trust described under Satisfaction and Discharge; Defeasance. The indenture requires us or the trustee to promptly notify holders of designated senior indebtedness if payment of subordinated debt securities is accelerated because of an event of default.

We may not make any payment on subordinated debt securities, including upon redemption at the option of the holder of any subordinated debt securities or at our option, if:

a default in the payment of the principal, premium, if any, interest, rent or other obligations in respect of designated senior indebtedness occurs and is continuing beyond any applicable period of grace (called a payment default); or

a default other than a payment default on any designated senior indebtedness occurs and is continuing that permits holders of designated senior indebtedness to accelerate its maturity, and the trustee receives notice of such default (called a payment blockage notice) from us or any other person permitted to give such notice under the indenture (called a non-payment default).

If the trustee or any holder of the notes receives any payment or distribution of our assets in contravention of the subordination provisions on subordinated debt securities before all senior indebtedness is paid in full in cash, property or securities, including by way of set-off, or other payment satisfactory to holders of senior indebtedness, then such payment or distribution will be held in trust for the benefit of holders of senior indebtedness or their representatives to the extent necessary to make payment in full in cash or payment satisfactory to the holders of senior indebtedness of all unpaid senior indebtedness.

In the event of our bankruptcy, dissolution or reorganization, holders of senior indebtedness may receive more, ratably, and holders of subordinated debt securities may receive less, ratably, than our other creditors (including our trade creditors). This subordination will not prevent the occurrence of any event of default under the indenture.

We are not prohibited from incurring debt, including senior indebtedness, under the indenture unless otherwise provided in the indenture. We may from time to time incur additional debt, including senior indebtedness.

We are obligated to pay reasonable compensation to the trustee and to indemnify the trustee against certain losses, liabilities or expenses incurred by the trustee in connection with its duties under the indenture. The trustee s claims for these payments will generally be senior to those of noteholders in respect of all funds collected or held by the trustee.

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Certain Definitions

indebtedness means:

(1) all indebtedness, obligations and other liabilities for borrowed money, including overdrafts, foreign exchange contracts, currency exchange agreements, interest rate protection agreements, and any loans or advances from banks, or evidenced by bonds, debentures, notes or similar instruments, other than any account payable or other accrued current liability or obligation incurred in the ordinary course of business in connection with the obtaining of materials or services;

(2) all reimbursement obligations and other liabilities with respect to letters of credit, bank guarantees or bankers acceptances;

(3) all obligations and liabilities in respect of leases required in conformity with generally accepted accounting principles to be accounted for as capitalized lease obligations on our balance sheet;

(4) all obligations and other liabilities under any lease or related document in connection with the lease of real property which provides that we are contractually obligated to purchase or cause a third party to purchase the leased property and thereby guarantee a minimum residual value of the leased property to the lessor and our obligations under the lease or related document to purchase or to cause a third party to purchase the leased property;

(5) all obligations with respect to an interest rate or other swap, cap or collar agreement or other similar instrument or agreement or foreign currency hedge, exchange, purchase or other similar instrument or agreement;

(6) all direct or indirect guaranties or similar agreements in respect of, and our obligations or liabilities to purchase, acquire or otherwise assure a creditor against loss in respect of, indebtedness, obligations or liabilities of others of the type described in (1) through (5) above;

(7) any indebtedness or other obligations described in (1) through (6) above secured by any mortgage, pledge, lien or other encumbrance existing on property which is owned or held by us; and

(8) any and all refinancings, replacements, deferrals, renewals, extensions and refundings of, or amendments, modifications or supplements to, any indebtedness, obligation or liability of the kind described in clauses (1) through (7) above.

permitted junior securities means (i) equity interests in the Company; or (ii) debt securities of the Company that are subordinated to all senior indebtedness and any debt securities issued in exchange for senior indebtedness to substantially the same extent as, or to a greater extent than the notes are subordinated to senior indebtedness under the indenture.

senior indebtedness means the principal, premium, if any, interest, including any interest accruing after bankruptcy, and rent or termination payment on or other amounts due on our current or future indebtedness, whether created, incurred, assumed, guaranteed or in effect guaranteed by us, including any deferrals, renewals, extensions, refundings, amendments, modifications or supplements to the above. However, senior indebtedness does not include:

indebtedness that expressly provides that it shall not be senior in right of payment to subordinated debt securities or expressly provides that it is on the same basis or junior to subordinated debt securities;

our indebtedness to any of our majority-owned subsidiaries; or

subordinated debt securities.

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DESCRIPTION OF WARRANTS

General

We may issue warrants for the purchase of our debt securities, preferred stock or common stock, or any combination thereof. Warrants may be issued independently or together with our debt securities, preferred stock or common stock and may be attached to or separate from any offered securities. Each series of warrants will be issued under a separate warrant agreement. We may enter into a warrant agreement with a bank or trust company, as warrant agent. We will indicate the name and address and other information regarding the warrant agent in the applicable prospectus supplement relating to a particular series of warrants. The warrant agent will act solely as our agent in connection with the warrants. The warrant agent will not have any obligation or relationship of agency or trust for or with any holders or beneficial owners of warrants. This summary of certain provisions of the warrants is not complete. For the terms of a particular series of warrants, you should refer to the prospectus supplement for that series of warrants and the warrant agreement for that particular series.

Debt Warrants

The prospectus supplement relating to a particular issue of warrants to purchase debt securities will describe the terms of the debt warrants, including the following:

the title of the debt warrants;

the offering price for the debt warrants, if any;

the aggregate number of the debt warrants;

the designation and terms of the debt securities, including any conversion rights, purchasable upon exercise of the debt warrants;

if applicable, the date from and after which the debt warrants and any debt securities issued with them will be separately transferable;

the principal amount of debt securities that may be purchased upon exercise of a debt warrant and the exercise price for the warrants, which may be payable in cash, securities or other property;

the dates on which the right to exercise the debt warrants will commence and expire;

if applicable, the minimum or maximum amount of the debt warrants that may be exercised at any one time;

whether the debt warrants represented by the debt warrant certificates or debt securities that may be issued upon exercise of the debt warrants will be issued in registered or bearer form;

information with respect to book-entry procedures, if any;

the currency or currency units in which the offering price, if any, and the exercise price are payable;

if applicable, a discussion of material U.S. federal income tax considerations;

the antidilution provisions of the debt warrants, if any;

the redemption or call provisions, if any, applicable to the debt warrants;

any provisions with respect to the holder s right to require us to repurchase the warrants upon a change in control or similar event; and

any additional terms of the debt warrants, including procedures, and limitations relating to the exchange, exercise and settlement of the debt warrants.

Debt warrant certificates will be exchangeable for new debt warrant certificates of different denominations. Debt warrants may be exercised at the corporate trust office of the warrant agent or any other office indicated in the prospectus supplement. Prior to the exercise of their debt warrants, holders of debt warrants will not have any of the rights of holders of the debt securities purchasable upon exercise and will not be entitled to payment of principal or

any premium, if any, or interest on the debt securities purchasable upon exercise.

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Equity Warrants

The prospectus supplement relating to a particular series of warrants to purchase our common stock or preferred stock will describe the terms of the warrants, including the following:

- the title of the warrants;
- the offering price for the warrants, if any;
- the aggregate number of warrants;
- the designation and terms of the common stock or preferred stock that may be purchased upon exercise of the warrants;
- if applicable, the designation and terms of the securities with which the warrants are issued and the number of warrants issued with each security;
- if applicable, the date from and after which the warrants and any securities issued with the warrants will be separately transferable;
- the number of shares of common stock or preferred stock that may be purchased upon exercise of a warrant and the exercise price for the warrants;
- the dates on which the right to exercise the warrants shall commence and expire;
- if applicable, the minimum or maximum amount of the warrants that may be exercised at any one time;
- the currency or currency units in which the offering price, if any, and the exercise price are payable;
- if applicable, a discussion of material U.S. federal income tax considerations;
- the antidilution provisions of the warrants, if any;
- the redemption or call provisions, if any, applicable to the warrants;
- any provisions with respect to holder s right to require us to repurchase the warrants upon a change in control or similar event; and
- any additional terms of the warrants, including procedures, and limitations relating to the exchange, exercise and settlement of the warrants.

Holders of equity warrants will not be entitled:

- to vote, consent or receive dividends;
- to receive notice as stockholders with respect to any meeting of stockholders for the election of our directors or any other matter; or
- to exercise any rights as stockholders of the Company.

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CERTAIN PROVISIONS OF DELAWARE LAW, THE CERTIFICATE OF INCORPORATION AND BYLAWS

Limitations on Directors Liability

Our certificate of incorporation and our bylaws contain provisions indemnifying our directors and officers to the fullest extent permitted by law. In addition, as permitted by Delaware law, our certificate of incorporation provides that no director will be liable to us or our stockholders for monetary damages for breach of certain fiduciary duties as a director. The effect of this provision is to restrict our rights and the rights of our stockholders in derivative suits to recover monetary damages against a director for breach of certain fiduciary duties as a director, except that a director will be personally liable for:

the benefits to be derived from relationships with our collaborators;
any breach of his or her duty of loyalty to the registrant or its stockholders;
acts or omissions not in good faith which involve intentional misconduct or a knowing violation of law;
the payment of dividends or the redemption or purchase of stock in violation of Delaware law; or
any transaction from which the director derived an improper personal benefit.
This provision does not affect a director s liability under the federal securities laws.

To the extent that our directors, officers and controlling persons are indemnified under the provisions contained in our certificate of incorporation, Delaware law or contractual arrangements against liabilities arising under the Securities Act, we have been advised that in the opinion of the Securities and Exchange Commission such indemnification is against public policy as expressed in the Securities Act, and is therefore unenforceable.

Provisions that May Have an Anti-Takeover Effect

Certain provisions set forth in our certificate of incorporation, bylaws and in Delaware law, which are summarized below, are intended to enhance the likelihood of continuity and stability in the composition of our Board of Directors and in the policies formulated by our Board of Directors and to discourage certain types of transactions that may involve an actual or threatened change of control. In that regard, these provisions are designed to reduce our vulnerability to an unsolicited acquisition proposal. The provisions also are intended to discourage certain tactics that may be used in proxy fights. However, such provisions could have the effect of discouraging others from making tender offers for our shares and, as a consequence, they also may inhibit fluctuations in the market price of our common stock that could result from actual or rumored takeover attempts. Such provisions also may have the effect of preventing changes in our management.

Blank Check Preferred Stock. Our certificate of incorporation contains provisions that permit our Board of Directors to issue, without any further vote or action by the stockholders, up to 30,000,000 shares of preferred stock in one or more series and, with respect to each such series, to fix the number of shares constituting the series and the designation of the series, the voting powers (if any) of the shares of the series, and the preferences and relative, participating, optional and other special rights, if any, and any qualifications, limitations or restrictions, of the shares of such series. As a result, our Board of Directors could authorize the issuance of shares of preferred stock with terms and conditions that could have the effect of delaying, deferring or preventing a transaction or a change in control that

might involve a premium price for holders of the registrant s common stock or otherwise be in their best interest.

Special Meetings of Stockholders. Our bylaws provide that special meetings of stockholders may be called only by the Board of Directors. Stockholders are not permitted to call a special meeting of stockholders or to require that the Board of Directors call such a special meeting.

Delaware Takeover Statute.

In general, Section 203 of the Delaware General Corporation Law prohibits a Delaware corporation that is a public company from engaging in any business combination (as defined below) with any interested stockholder (defined generally as an entity or person beneficially owning 15% or more of the outstanding

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voting stock of the corporation and any entity or person affiliated with such entity or person) for a period of three years following the date that such stockholder became an interested stockholder, unless: (1) 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; (2) on 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 (x) by persons who are directors and also officers and (y) 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 (3) 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 of the Delaware General Corporation Law defines business combination to include: (1) any merger or consolidation involving the corporation and the interested stockholder; (2) any sale, transfer, pledge or other disposition of 10% or more of the assets of the corporation involving the interested stockholder; (3) 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; (4) 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 (5) 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.

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WHERE YOU CAN FIND MORE INFORMATION

We are a reporting company and file annual, quarterly and current reports, proxy statements and other information with the SEC. You may read and copy these reports, proxy statements and other information at the SEC s public reference room at 100 F. Street, N.E., Washington, D.C. 20549 or at the SEC s other public reference facilities. Please call the SEC at 1-800-SEC-0330 for more information about the operation of the public reference rooms. You can request copies of these documents by writing to the SEC and paying a fee for the copying costs. In addition, the SEC maintains an Internet site at *http://www.sec.gov* that contains reports, proxy and information statements and other information regarding issuers that file electronically with the SEC. Our SEC filings are available on the SEC s Internet site.

INCORPORATION OF CERTAIN INFORMATION BY REFERENCE

We are allowed to incorporate by reference information contained in documents that we file with the SEC. This means that we can disclose important information to you by referring you to those documents and that the information in this prospectus is not complete and you should read the information incorporated by reference for more detail. We incorporate by reference in two ways. First, we list certain documents that we have already filed with the SEC. The information in these documents is considered part of this prospectus. Second, the information in documents that we file in the future will update and supersede the current information in, and incorporated by reference in, this prospectus.

We incorporate by reference the documents listed below and any future filings we will make with the SEC under Section 13(a), 13(c), 14 or 15(d) of the Securities Exchange Act of 1934, as amended, or the Exchange Act (other than information furnished in Current Reports on Form 8-K filed under Item 2.02 or 7.01 of such form), including filings made after the date of the initial registration statement of which this prospectus is a part and prior to the effective date of such registration statement:

Annual Report on Form 10-K for the fiscal year ended December 31, 2009, filed on March 17, 2010, as amended by Amendment No. 1 to Annual Report on Form 10-K/A filed on April 30, 2010;

Quarterly Report on Form 10-Q for the quarter ended March 31, 2010, filed on April 30, 2010;

Current Reports on Form 8-K filed on January 27, 2010 and April 6, 2010; and

The description of our common stock set forth in the registration statement on Form 8-A registering our common stock under Section 12 of the Exchange Act, which was filed with the SEC on September 20, 2006.

We will provide to each person, including any beneficial owner, to whom a prospectus is delivered, a copy of any or all of the information that has been incorporated by reference in this prospectus but not delivered with this prospectus. You may request a copy of this information at no cost, by writing or telephoning us at the following address or telephone number:

ZIOPHARM Oncology, Inc.
1180 Avenue of the Americas, 19th Floor
New York, NY 10036
Attention: President
Telephone: (646) 214-0700

You should rely only on the information incorporated by reference or provided in this prospectus or any supplement. We have not authorized anyone else to provide you with different information. The selling stockholders will not make an offer of these shares in any state where the offer is not permitted. You should not assume that the information in this prospectus or any supplement is accurate as of any date other than the date on the front of these documents.

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LEGAL MATTERS

The validity of the securities offered hereby will be passed upon by Maslon Edelman Borman & Brand, LLP, Minneapolis, Minnesota.

EXPERTS

The balance sheets of ZIOPHARM Oncology, Inc. as of December 31, 2009 and 2008 and the related statements of operations, changes in convertible preferred stock and stockholders equity (deficit) and cash flows for each of the years in the three-year period ended December 31, 2009 and for the period from September 9, 2003 (date of inception) through December 31, 2009, included in this prospectus, have been included herein in reliance on the report, dated March 17, 2010, of Caturano and Company, P.C., independent registered public accounting firm, (which report expresses an unqualified opinion and includes an explanatory paragraph relating to the change in the manner in which the Company accounts for certain warrants), given on the authority of that firm as experts in auditing and accounting.

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9,600,000 Shares

Common Stock

Prospectus Supplement
February 3, 2011

Barclays Capital