

ZIOPHARM ONCOLOGY INC
Form 10-K
February 29, 2012

**UNITED STATES
SECURITIES AND EXCHANGE COMMISSION
Washington, DC 20549**

FORM 10-K

x ANNUAL REPORT UNDER SECTION 13 OR 15(d)
OF THE SECURITIES EXCHANGE ACT OF 1934
For the fiscal year ended December 31, 2011

OR

o TRANSITION REPORT UNDER SECTION 13 OR 15(d)
OF THE SECURITIES EXCHANGE ACT OF 1934
For the transition period from to
Commission File Number 001-33038

ZIOPHARM Oncology, Inc.

(Exact Name of Registrant as Specified in Its Charter)

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Delaware
(State or Other Jurisdiction of
Incorporation or Organization)
1180 Avenue of the Americas, 20th Floor, New York, NY
(Address of Principal Executive Offices)

84-1475642
(IRS Employer
Identification No.)
10036
(Zip Code)

(646) 214-0700

(Issuer's Telephone Number, Including Area Code)

(Former Name, Former Address and Former Fiscal Year, if Changed Since Last Report)

Securities registered pursuant to Section 12(b) of the Act:
Common Stock (par value \$0.001 per share)

Indicate by check mark if the registrant is a well-known seasoned issuer, as defined in Rule 405 of the Securities Act.
Yes No

Indicate by check mark if the registrant is not required to file reports pursuant to Section 13 or 15(d) of the Act. Yes No

Indicate by check mark whether the registrant (1) has filed all reports required to be filed by Section 13 or 15(d) of the Securities Exchange Act of 1934 during the past 12 months (or for such shorter period that the registrant was required to file such reports), and (2) has been subject to such filing requirements for the past 90 days. Yes No

Indicate by check mark whether the registrant has submitted electronically and posted on its corporate Web site, if any, every Interactive Data File required to be submitted and posted pursuant to Rule 405 of Regulation S-T during the preceding 12 months (or for such shorter period that the registrant was required to submit and post such files). Yes No

Indicate by check mark if disclosure of delinquent filers pursuant to Item 405 of Regulation S-K is not contained herein, and will not be contained, to the best of registrant's knowledge, in definitive proxy or information statements incorporated by reference in Part III of this Form 10-K or any amendment to this Form 10-K.

Indicate by check mark whether the registrant is a large accelerated filer, an accelerated filer, a non-accelerated filer or a smaller reporting company. See definition of large accelerated filer, accelerated filer and smaller reporting company in Rule 12b-2 of the Exchange Act. (Check one):

Large Accelerated Filer Accelerated Filer Non-Accelerated Filer Smaller Reporting Company
Indicate by check mark whether the registration is a shell company (as defined in Rule 12b-2 of the Act). Yes No

The aggregate market value of the registrant's common stock held by non-affiliates was \$316,081,207 as of June 30, 2011 (the last business day of the registrant's most recently completed second fiscal quarter), based on a total of 51,647,256 shares of common stock held by non-affiliates and on a closing price of \$6.12 as reported on the NASDAQ Capital Market on June 30, 2011.

As of February 15, 2012, there were 79,472,777 shares of the registrant's common stock, \$.001 par value per share, outstanding.

DOCUMENTS INCORPORATED BY REFERENCE:

Portions of the definitive proxy statement for our 2012 annual meeting of stockholders, which is to be filed within 120 days after the end of the fiscal year ended December 31, 2011, are incorporated by reference into Part III of this Form 10-K, to the extent described in Part III.

TABLE OF CONTENTS

ZIOPHARM Oncology, Inc.
(a development stage enterprise)

FORM 10-K
FOR THE FISCAL YEAR ENDED DECEMBER 31, 2011

TABLE OF CONTENTS

	Page
PART I	
<u>Item 1.</u>	1
<u>Business</u>	
<u>Item 1A.</u>	18
<u>Risk Factors</u>	
<u>Item 1B.</u>	32
<u>Unresolved Staff Comments</u>	
<u>Item 2.</u>	32
<u>Properties</u>	
<u>Item 3.</u>	32
<u>Legal Proceedings</u>	
<u>Item 4.</u>	32
<u>Mine Safety Disclosure</u>	
PART II	
<u>Item 5.</u>	33
<u>Market for Registrant's Common Equity, Related Stockholder Matters and Issuer Purchases of Equity Securities</u>	
<u>Item 6.</u>	34
<u>Selected Financial Data</u>	
<u>Item 7.</u>	35
<u>Management's Discussion and Analysis of Financial Condition and Results of Operations</u>	

<u>Item 7A.</u>	<u>44</u>
<u>Quantitative and Qualitative Disclosures About Market Risk</u>	
<u>Item 8.</u>	<u>45</u>
<u>Financial Statements and Supplementary Data</u>	
<u>Item 9.</u>	<u>45</u>
<u>Changes in and Disagreements with Accountants on Accounting and Financial Disclosures</u>	
<u>Item 9A.</u>	<u>45</u>
<u>Controls and Procedures</u>	
<u>Item 9B.</u>	<u>45</u>
<u>Other Information</u>	
PART III	
<u>Item 10.</u>	<u>46</u>
<u>Directors, Executive Officers and Corporate Governance</u>	
<u>Item 11.</u>	<u>46</u>
<u>Executive Compensation</u>	
<u>Item 12.</u>	<u>46</u>
<u>Security Ownership of Certain Beneficial Owners and Management and Related Stockholder Matters</u>	
<u>Item 13.</u>	<u>46</u>
<u>Certain Relationships and Related Transactions, and Director Independence</u>	
<u>Item 14.</u>	<u>46</u>
<u>Principal Accountant Fees and Services</u>	
PART IV	
<u>Item 15.</u>	<u>47</u>
<u>Exhibits and Financial Statement Schedules</u>	
<u>Signatures</u>	<u>48</u>
<u>Financial Statements</u>	<u>F-1</u>
<u>Exhibit Index</u>	<u>A-1</u>

Our registered trademarks include Zymafos and Zinapar. Our trademarks include Zybulin. All other trademarks, trade names and service marks appearing in this annual report on Form 10-K are the property of their respective owners.

TABLE OF CONTENTS

PART I

Item 1. Business

General

ZIOPHARM Oncology, Inc. is a biopharmaceutical company that seeks to develop and commercialize a diverse portfolio of cancer drugs that can address unmet medical needs. Our principal focus was initially 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, or IV, and/or oral dosing. Our clinical programs for our small molecule candidates include palifosfamide (Zymafos or ZIO-201), darinaparsin (Zinapar or ZIO-101) and indibulin (Zybulin or ZIO-301). We are also pursuing the development of novel DNA-based biotherapeutics in the field of cancer pursuant to a partnering arrangement with Intrexon Corporation, or Intrexon.

Under the arrangement, we obtained rights to Intrexon's effector platform for use in the field of oncology, which includes two existing clinical stage product candidates, ZIN-CTI-001 (or DC-RTS-IL-12 + AL) and ZIN-ATI-001 (or Ad-RTS-IL-12 + AL). We plan to leverage Intrexon's synthetic biology platform to develop products to inhibit the growth and metastasis of cancers, adding significantly to our candidate portfolio.

We believe that our strategy will result in expedited drug development programs for product candidates that would include a cost of development and manufacturing that, upon successful commercialization, would address changing worldwide product reimbursement requirements. We are currently in Phase 1, 2, and/or Phase 3 studies for our product candidates with our lead palifosfamide program completing enrollment in a global pivotal Phase 3 trial to support registration in combination with doxorubicin in the front-line setting of metastatic soft tissue sarcoma, or STS.

More detailed descriptions of palifosfamide, darinaparsin, indibulin, ZIN-CTI-001 and ZIN-ATI-001, and our clinical development plans for each, are set forth in this report under the caption Business Product Candidates.

Cancer Overview

Cancer is a group of diseases characterized by either the runaway growth of cells or the failure of cells to die normally. Often, cancer cells spread to distant parts of the body, where they can form new tumors. Cancer can arise in any organ of the body and, according to the American Cancer Society, strikes slightly less than one of every two American men and a little more than one of every three American women at some point in their lives.

It is reported that there are more than 100 different varieties of cancer. Carcinomas, the most common type of cancer, originate in tissues that cover a surface or line a cavity of the body. Lymphomas are cancers of the lymph system, which is a circulatory system that bathes and cleanses the body's cells. Leukemias involve blood-forming tissues and blood cells. As their name indicates, brain tumors are cancers that begin in the brain, skin cancers, including melanomas, originate in the skin, while STS arises in soft tissue. Cancers are considered metastatic if they spread through the blood or lymphatic system to other parts of the body to form secondary tumors.

Cancer is caused by a series of mutations (alterations) in genes that control cells' ability to grow and divide. Some mutations are inherited; others arise from environmental factors such as smoking or exposure to chemicals, radiation, or viruses that damage cells' DNA. The mutations cause cells to divide relentlessly or lose their normal ability to die.

According to the American Cancer Society, it is estimated that about 1,638,910 new cases of cancer were expected to be diagnosed in 2012 and about 577,190 Americans will die from cancer in 2012 more than 1,500 each day. The cost of treating cancer is significant. The National Institute of Health estimates that the overall costs of cancer in 2007 were \$226.8 billion. These costs included an estimate of \$103.8 billion in direct medical costs and \$123.0 billion in indirect mortality costs.

Cancer Treatments

Major treatments for cancer include surgery, radiotherapy, and chemotherapy; the latter including newer approaches such as anti-angiogenic, vascular disruption and targeted therapies. Also associated with the

1

TABLE OF CONTENTS

treatment of cancer is supportive care; and recently, immunological-based approaches have proved to be of benefit either alone or in combination. While there are also hundreds of experimental treatments under investigation, including DNA and other immunological based therapies, we believe cancer treatment will remain a significant unmet medical need for the foreseeable future.

Radiotherapy: Also called radiation therapy, radiotherapy is the treatment of cancer and other diseases with ionizing radiation. Ionizing radiation deposits energy that injures or destroys cells in the area being treated (the target tissue) by damaging their genetic material, making it impossible for these cells to continue growing. Although radiation damages both cancer cells and normal cells, the latter are able to repair and regain proper function. Radiotherapy may be used to treat localized solid tumors such as cancers of the skin, tongue, larynx, brain, breast, or uterine cervix. It can also be used to treat leukemia and lymphoma.

Scientists are also looking for ways to increase the effectiveness of radiation therapy. Two types of investigational drugs are being studied for their effect on cells exposed to radiation. Radiosensitizers increase the damage done to tumor cells by radiation; radioprotectors protect normal tissues from the effects of radiation.

Chemotherapy: Chemotherapy is the treatment of cancer with cytotoxics, which are anti-cancer drugs that destroy cancer cells by stopping them from multiplying. Healthy cells, especially those that divide quickly, can also be harmed with the use of cytotoxics. Harm to healthy cells is what causes side effects. These cells usually repair themselves after chemotherapy and in many cases, newer agents may offer a greater therapeutic window the difference between a dose that is helpful and one that is toxic often referred to as targeted therapies.

Cytotoxic agents act primarily by disrupting cellular pathways involved in maintaining cellular integrity including blood supply, repair, or activity that affects the production or function of DNA, RNA, or protein. Although there are many cytotoxic agents, there is a considerable overlap in their mechanisms of action. As such, the choice of a particular agent or group of agents is generally not a consequence of a prior prediction of anti-tumor activity by the drug, but instead the result of empirical clinical trials.

Immunological and DNA-based approaches: The approval of Bristol-Meyers Squibb's YERVOY™ (ipilimumab) for melanoma, validated an immune-based approach and has opened the full exploration of harnessing the immune system to treat cancer. Strategies that are synthetic biology or otherwise DNA-based, including the approach by Intrexon, are in clinical development, providing a further promising new avenue to treat cancer.

Supportive Care: Cancer treatments are directed at killing or eradicating the cancer that exists in a patient's body. Unfortunately, the delivery of many cancer therapies adversely affects the body's normal organs. The undesired consequence of harming an organ not involved with cancer is referred to as a complication of treatment or a side effect.

In addition to anemia, fatigue, hair-loss, reduction in blood platelets and white and red blood cells, and bone pain, two of the most common side effects of chemotherapy are nausea and vomiting. Several drugs have been developed to help prevent and control chemotherapy-induced nausea and vomiting, including 5HT₃ receptor antagonists such as ondansetron, which is a selective blocking agent of the hormone serotonin.

Product Candidates

Palifosfamide, Zymafos, ZIO-201

General. Palifosfamide, or isophosphoramidate mustard (IPM), is a proprietary active metabolite of the pro-drug ifosfamide. Ifosfamide, like the related drugs cyclophosphamide and bendamustine, is a DNA alkylating agent, which is a form of cancer therapy to treat a wide range of solid tumors and hematological malignancies. Ifosfamide has been shown to be effective in the treatment of sarcoma and lymphoma, either by itself or in combination with other anti-cancer agents. Ifosfamide is approved by the U.S. Food and Drug Administration, or FDA, as a treatment for testicular cancer and often used in combination to treat sarcoma, although it is not approved for this indication by the FDA.

Our preclinical studies have shown that, in animal and laboratory models, palifosfamide evidences activity against leukemia and solid tumors. These studies also indicate that palifosfamide may have a better

TABLE OF CONTENTS

safety profile than ifosfamide or cyclophosphamide, in part 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. Because palifosfamide is the stabilized active metabolite of ifosfamide and a distinct pharmaceutical composition and without the acrolein or chloroacetaldehyde metabolites, we believe that the administration of palifosfamide may be a new, more effective and a better tolerated agent to treat cancer.

In addition to anticipated lower toxicity, palifosfamide may have other advantages over ifosfamide and cyclophosphamide. Palifosfamide cross-links DNA differently than the active metabolite of cyclophosphamide, resulting in a different activity profile. Moreover, in some preclinical studies, palifosfamide has been shown to bypass resistance mediated by aldehyde dehydrogenase (ALDH), an enzyme thought to confer resistance to alkylators like ifosfamide and cyclophosphamide. 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.

Lead Indications for palifosfamide: Soft Tissue Sarcoma. Sarcomas are cancers of the bone, cartilage, fat, muscle, blood vessels, or other connective or supportive tissue. There are more than 50 histological or tissue types of STSs but with considerable homogeneity when the disease is metastatic. The prognosis for patients with soft tissue sarcoma depends on several factors, including the patient's age, size of the primary tumor, histological grade, and stage of the tumor. Factors associated with a poorer prognosis include being older than 60 years of age, having tumors larger than five centimeters, and having tumors of high-grade histology. While small, low-grade tumors are usually curable by surgery alone, the higher-grade or larger sarcomas are associated with higher local treatment failure rates and increased metastatic potential.

Intravenous palifosfamide may be a useful agent that, either alone or in combination with other agents and doxorubicin in particular, may deliver enhanced therapeutic activity with fewer side effects of the type that have been associated with ifosfamide. In the United States, ifosfamide is often included in combination regimens for the treatment of sarcomas, testicular cancers, head and neck cancer, certain types of non-Hodgkin's lymphomas, and other solid tumors including small-cell lung cancer, or SCLC, although it is not formally approved by FDA for the treatment of soft tissue sarcoma. Doxorubicin, approved decades ago, is the only FDA-approved treatment for sarcoma. We believe that palifosfamide in combination with doxorubicin may be more effective than doxorubicin alone and with a far improved safety profile and impact on Quality of Life (QoL) over the combination of ifosfamide use with doxorubicin.

Small-Cell Lung Cancer. SCLC is almost exclusively associated with smoking. Similar to sarcoma, standard of care for SCLC, which is etoposide and platinum therapy, has changed little in decades. Published studies of ifosfamide in combination with standard of care have evidenced enhanced efficacy but also with enhanced side effects, providing for an unfavorable benefit to risk association. We believe that combining palifosfamide with standard of care could offer a separation of enhanced efficacy from increased toxicity.

Other Indications. Palifosfamide may be useful to treat many other solid tumors, including pediatric cancer, and hematological malignancies. With an investigational new drug (IND) application for the oral form of palifosfamide now approved by FDA, the treatment could also offer not only a significant advancement to current therapies but also greater patient access and convenience.

Lead Indications for palifosfamide: STS and SCLC, Significant Unmet Medical Need. Both front-line metastatic soft tissue sarcoma and extensive SCLC represent significant unmet medical needs with standard of care considerably dated. We believe approximately 100,000 patients worldwide are initially diagnosed with STS every year. For patients diagnosed with STS, primary care is surgery, sometimes with radiation therapy. Many patients enter a period of remission that is unpredictable and can even represent a cure. Metastatic STS arises when the disease has re-occurred and surgery is no longer an option. Chemotherapy is the standard of care for front-line metastatic STS and doxorubicin is the only front-line therapy approved in the United States for its treatment. We believe the annual projection in the United States for front-line metastatic STS treatment is approximately 9,000 patients. While data sources for Europe are limited, we estimate, based on

TABLE OF CONTENTS

epidemiology, an annual projection in Europe for front-line metastatic STS treatment of approximately 14,000 patients, for a combined U.S. and European estimate of 23,000 patients annually. Orphan Drug Designation for palifosfamide has been obtained in both the United States and the European Union for the treatment of STS. For SCLC, the estimated U.S. annual incidence is 30-35,000 patients and 200,000 patients worldwide. Approximately 80-90% of patients have extensive disease, the population for the planned pivotal trial. Platinum and etoposide are standard of care in the front-line setting. A formal retrospective mortality study also suggests that the SCLC population in China is substantial and projected from the study to be greater than 150,000 patients and growing.

Clinical Development Plan for Palifosfamide. With IV administration and following Phase 1 study, we completed Phase 2 testing of palifosfamide as a single agent to treat advanced sarcoma. In both Phase 1 and Phase 2 testing, palifosfamide has been administered without the uroprotectant mesna, as is required with ifosfamide, and the toxicities associated with other ifosfamide metabolites, acrolein and chloroacetaldehyde, have not been observed. We reported clinical activity of palifosfamide when used alone in the Phase 2 study addressing advanced sarcoma. Following review of preclinical combination studies, we initiated a Phase 1 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 2 single agent clinical activity data and with the combination being well tolerated in the Phase 1 trial, we initiated a Phase 2 randomized controlled trial in the second half of 2008, which we refer to as PICASSO, to compare doxorubicin plus palifosfamide to doxorubicin alone in patients with front- and second-line metastatic or unresectable STS. 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 our 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 in June 2010, where the presentation was 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 2 meeting and the Special Protocol Assessment, or SPA, process. Although we did engage in the SPA process, we, with guidance from the FDA, elected to initiate the trial without having obtained SPA agreement from the FDA. The Phase 3 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. PICASSO 3 has no interim efficacy analysis, while the trial is monitored by an Independent Data Monitoring Committee, or IDMC, of outside, independent experts for safety and futility. The IDMC has met on three occasions to review all available study data and in all instances has recommended trial continuation. Orphan Drug Designation for palifosfamide has been obtained in both the United States and the European Union for the treatment of STS.

Subsequent to year-end 2011, we announced in February positive preliminary overall survival, or OS, data from our randomized, controlled Phase 2 PICASSO trial. An analysis of the OS data, conducted according to the statistical analysis plan and with greater than 70% of events occurring, demonstrated a positive Intent to Treat (ITT) hazard ratio of 0.79 and a modified Intent to Treat (mITT) hazard ratio of 0.78. At 2-years after starting treatment, approximately 40% of subjects treated with palifosfamide are alive; 30% in the control arm treated with doxorubicin (including those who crossed-over and received subsequent palifosfamide) are alive, compared to an expected 25% based on historical data. The OS analysis and the earlier PFS reported results show correlation between the two with the results fully confirming the modeling and powering of the ongoing Phase 3 trial (PICASSO 3) for both progression-free survival for accelerated approval and OS for full approval.

A Phase 1 trial has completed accrual with palifosfamide in combination with etoposide and carboplatin to determine appropriate safety for initiating a potentially pivotal, adaptive Phase 3 trial in front-line, extensive SCLC expected to initiate in the second half of 2012. An oral form of palifosfamide has been the subject of preclinical studies necessary for an Investigational New Drug, or IND, application to support

TABLE OF CONTENTS

commencing Phase 1 study. Based on an initial review, the FDA requested that we repeat an animal study, which was completed and submitted to the FDA in January 2012. The IND for the oral formulation was approved in February 2012.

DNA-based therapeutics (synthetic biology) ZIN-CTI-001 (or DC-RTS-IL-12 + AL) and ZIN-ATI-001 (or Ad-RTS-IL-12 + AL)

General. On January 6, 2011, we entered into an Exclusive Channel Partner Agreement with Intrexon pursuant to which we plan to 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. The channel partnering arrangement contemplates our using Intrexon's technology directed towards *in vivo* expression of effectors in connection with the development of ZIN-CTI-001 and ZIN-ATI-001 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. See *License Agreements, Intellectual Property and Other Agreements - Exclusive Channel Partner Agreement with Intrexon Corporation* below. ZIN-CTI-001 (or DC-RTS-IL-12) and ZIN-ATI-001 (or Ad-RTS-IL-12) are the two existing clinical-stage products currently in development under this channel partnering arrangement. Under the arrangement, Intrexon assigned to us all regulatory filings and approvals relating to the two product candidates and we assumed sponsorship of the ongoing clinical trials of ZIN-CTI-001.

Clinical Development Plan for DNA-based therapeutics. ZIN-CTI-001 is in a Phase 1b trial in the United States and employs intratumoral injection of modified dendritic cells from each patient and oral dosing of an activator ligand to turn on *in vivo* expression of interleukin-12, or IL-12. ZIN-CTI-001, through the RheoSwitch Therapeutic System®, or RTS, controls the timing and level of transgene expression. The RTS technology 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 Phase 1 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 International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use 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 animal. Preclinical studies have shown DC-RTS-IL-12, in combination with an activator ligand, to have strong activity against a broad array of cancers, including brain, colon, renal and pancreatic cancers and melanoma.

A Phase 1a 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. A subsequent Phase 1b trial, which is ongoing in patients with advanced melanoma, 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. Initial positive clinical results from the Phase 1b trial were presented at the June 2011 ASCO annual meeting. The trial enrolled ten patients (median age 61) with unresectable Stage III or IV melanoma. Among eight evaluable patients, partial or complete regression of injected and some uninjected lesions was observed by computed axial tomography, or CT, scans in three patients, with >11 months and three patients demonstrating stable disease by RECIST, for an overall disease control rate of 50%. Treatment was generally well tolerated, and maximum tolerated dose has not yet been reached. Adverse events were mild to moderate, with one to two patients each experiencing nausea, vomiting, anorexia, arthralgia, fever or chills. One severe adverse event was reported 18 hours after treatment onset with 60 mg

AL + ZIN-CTI-001, and included diarrhea, followed by hypotension and reversible acute renal failure, which completely resolved.

TABLE OF CONTENTS

Clinical study of ZIN-ATI-001, essentially ZIN-CTI-001 without dendritic cells, has also initiated in Phase 1 study in advanced melanoma. The Phase 1 study will evaluate safety in addition to immunological and biological effects and efficacy of the therapeutic candidate in patients with melanoma.

We intend to evaluate both ZIN-CTI-001 and ZIN-ATI-001 with the intent to advance ZIN-ATI-001 into at least two Phase 2 trials, one a potentially pivotal trial for accelerated approval in an indication with significant unmet medical need.

We are also in late preclinical evaluation with respect to several additional potential product candidates under our channel partnership with Intrexon, and we anticipate continuing evaluation to select product candidates for clinical study, which could commence as early as this year. We also anticipate continuing discovery efforts aimed at identifying additional potential product candidates under the Intrexon channel partnership for study thereafter.

Indibulin, Zybulin, ZIO-301

General. Indibulin 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 those in 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 anti-cancer 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 broad 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 1 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.

Indibulin has a different pharmacological profile from other tubulin inhibitors currently on the market as it binds to a unique site on tubulin and is active in multi-drug-resistant (MDR-1, MRP-1) and taxane-resistant tumors. Indibulin binding causes destabilization of microtubules *in vitro*, an effect similar to that of the vinca alkaloid family or colchicine, but opposite to that of paclitaxel and related drugs and different from the epothilones.

Testing of indibulin for *in vitro* growth inhibitory activity against a panel of human and rodent tumor-derived cell lines revealed that the drug candidate is active in a broad spectrum of cell lines derived from different organs. *In vivo*, indibulin is active in a number of xenograft and rodent tumor models. Its unique pharmacodynamic properties demonstrated in preclinical studies, as well as an excellent safety profile observed thus far in ongoing Phase 1 studies, warrant further evaluation in the clinic.

Clinical Development Plan for Indibulin. Phase 1 study as a single agent in patients with advanced solid tumors has been completed. We have reported clinical activity at well-tolerated doses using a continuous dosing scheme without the development of clinically relevant peripheral neuropathy. Following encouraging preclinical results obtained with indibulin in combination with other chemotherapies, two Phase 1 combination studies were initiated with Tarceva™ and Xeloda™, respectively. The favorable activity and safety profile of oral indibulin with oral Xeloda™ was reported at ASCO's annual meeting in May 2009. In all studies, a maximum tolerated dose, or MTD, has not been established. Preclinical work with our consultant established a dosing schedule to enhance activity, while managing toxicity and that regimen, five days on drug and nine days off, is now in Phase 1 study in late stage metastatic breast cancer. In light of the lack of establishing an

TABLE OF CONTENTS

MTD and the need to administer many capsules several times a day, we have recently modified the dosage form to administer once a day dosing in the Phase 1 trial.

Darinaparsin, Zinapar, ZIO-101

General. Darinaparsin is an anti-mitochondrial (organic arsenic) compound covered by issued patents and pending patent applications in the United States 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 electrocardiogram 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, providing support for the development of an oral form of the drug, and established synergy of darinaparsin in combination with other approved anti-cancer agents.

Potential Lead Indication: Lymphoma. Three Phase 2 intravenous, or IV studies of IV darinaparsin evaluating hematological malignancies, myeloma and liver cancer, have been completed and data from these trials has been reported, the most promising being in lymphomas and particularly in peripheral T-cell lymphoma.

Clinical Development Plan for darinaparsin: Phase 1 testing of the IV form of darinaparsin in solid tumors and hematological cancers was completed and we reported clinical activity and, we believe importantly, a safety profile from these studies as predicted by preclinical results. We subsequently completed Phase 2 studies in advanced myeloma, primary liver cancer and in certain other hematological cancers. At the May 2009 annual meeting of the American Society of Clinical Oncology, or ASCO, we reported favorable results from the IV trial in lymphoma, particularly peripheral T-cell lymphoma, or PTCL. With a subsequent focus on the relapsed setting of PTCL, a Phase 1 study of darinaparsin in combination with the treatment regimen called CHOP in the front-line setting of PTCL was ended. A Phase 1 trial in solid tumors with an oral form of darinaparsin is nearing completion. Data from the Phase 1 oral study will guide further study. We have obtained Orphan Drug Designation for darinaparsin in the United States and Europe for the treatment of PTCL and have entered into a licensing agreement with Solasia for the Asia/Pacific territory with a focus on IV-administered darinaparsin in PTCL.

TABLE OF CONTENTS

Competition

The development and commercialization for new products to treat cancer, including for both the targeted indications of STS and SCLC for palifosfamide, is highly competitive, and considerable competition exists from major pharmaceutical, biotechnology, and specialty cancer companies. Several of our competitors have access to substantially greater financial and technical resources than we do and, even if we are successfully developing and commercializing palifosfamide, these competitors have or can market products that could adversely impact the commercial success or potential of commercial success of these product candidates. In addition, many of these companies have more experience in preclinical and clinical development, manufacturing, regulatory, and global commercialization. We are also competing with academic institutions, governmental agencies, and private organizations that are conducting research in the field of cancer. Competition for highly qualified employees and their retention is intense, particularly as companies adjust to the current economic environment.

Other treatments for cancer that compete with our product candidates are summarized under the caption **Cancer Treatments** above.

License Agreements, Intellectual Property and Other Agreements.

Our goal is to obtain, maintain, and enforce patent protection for our products, formulations, processes, methods, and other proprietary technologies in order to preserve our trade secrets and to operate without infringing upon the proprietary rights of other parties. Our policy is to actively seek the broadest possible intellectual property protection for our product candidates through a combination of contractual arrangements and patents, both in the United States and abroad.

Patent and Technology License Agreement The University of Texas M. D. Anderson Cancer Center and the Texas A&M University System.

On August 24, 2004, we entered into a patent and technology license agreement with The Board of Regents of the University of Texas System, acting on behalf of The University of Texas M. D. Anderson Cancer Center and the Texas A&M University System, which we refer to, collectively, as the Licensors. Under this agreement, we were granted an exclusive, worldwide license to rights (including rights to U.S. and foreign patent and patent applications and related improvements and know-how) for the manufacture and commercialization of two classes of organic arsenicals (water- and lipid-based) for human and animal use. The class of water-based organic arsenicals includes darinaparsin.

As partial consideration for the license rights obtained, we made an upfront payment in 2004 of \$125 thousand and granted the Licensors 250,487 shares of our common stock. In addition, we issued options to purchase an additional 50,222 shares outside our 2003 Stock Option Plan for \$0.002 per share following the successful completion of certain clinical milestones, which vested with respect to 12,555 shares upon the filing of an IND for darinaparsin in 2005 and vested with respect to another 25,111 shares upon the completion of dosing of the last patient for both Phase 1 clinical trials in 2007. We recorded \$120 thousand of stock-based compensation expense related to the vesting in 2007. The remaining 12,556 shares will vest upon enrollment of the first patient in a multi-center pivotal clinical trial i.e. a human clinical trial intended to provide the substantial evidence of efficacy necessary to support the filing of an approvable New Drug Application, or NDA. In addition, the Licensors are entitled to receive certain milestone payments, including \$100 thousand that was paid in 2005 upon the commencement of Phase 1 clinical trial and \$250

thousand that was paid in 2006 upon the dosing of the first patient in our Phase 2 clinical trial for darinaparsin. We may be required to make additional payments upon achievement of certain other milestones in varying amounts which on a cumulative basis could total up to an additional \$4.5 million. In addition, the Licensors are entitled to receive single digit percentage royalty payments on sales from a licensed product and will also be entitled to receive a portion of any fees that we may receive from a possible sublicense under certain circumstances. In addition, we paid the Licensors \$100 thousand in 2006 and 2007 to conduct scientific research with us obtaining exclusive right to all resulting intellectual property rights. The sponsored research agreements governing this research and any related extensions expired in February 2008 with no payments being made subsequent to that date.

TABLE OF CONTENTS

The license agreement also contains other provisions customary and common in similar agreements within the industry, such as the right to sublicense our rights under the agreement. However, if we sublicense our rights prior to the commencement of a pivotal study, which is a human clinical trial intended to provide the substantial evidence of efficacy necessary to support the filing of an approvable NDA, the Licensors will be entitled to receive a share of the payments received by us in exchange for the sublicense (subject to certain exceptions). The term of the license agreement extends until the expiration of all claims under patents and patent applications associated with the licensed technology, subject to earlier termination in the event of defaults by us or the Licensors under the license agreement, or if we become bankrupt or insolvent. No milestones under the license agreement were reached or expensed during the years ended December 31, 2009, 2010 or 2011.

License Agreement with DEKK-Tec, Inc.

On October 15, 2004, we entered into a license agreement with DEKK-Tec, Inc., pursuant to which we were granted an exclusive, worldwide license for palifosfamide. As part of the signing of license agreement with DEKK-Tec, we expensed an upfront \$50 thousand payment to DEKK-Tec in 2004.

In consideration for the license rights, DEKK-Tec is entitled to receive payments upon achieving certain milestones in varying amounts which on a cumulative basis may total \$4.0 million. Of the aggregate milestone payments, most will be creditable against future royalty payments as discussed below. We expensed a \$100 thousand milestone payment upon achieving Phase 2 milestones during the year ended December 31, 2006. Additionally, in 2004 we issued DEKK-Tec an option to purchase 27,616 shares of our common stock for \$0.02 per share. Upon the execution of the license agreement, 6,904 shares vested and were subsequently exercised in 2005 and the remaining options will vest upon certain milestone events, culminating with final FDA approval of the first NDA submitted by us (or by our sublicensee) for palifosfamide. DEKK-Tec is entitled to receive single digit percentage royalty payments on the sales of palifosfamide should it be approved for commercial sale. On March 16, 2010, we expensed a \$100 thousand milestone payment upon receiving a U.S. patent for palifosfamide. There were no payments made during 2009. In December 2010, we expensed a \$300 thousand milestone payment and vested 6,904 stock options upon achieving Phase 3 milestones. These options were subsequently exercised in 2011. Our obligation to pay royalties will terminate on a country-by-country basis upon the expiration of all valid claims of patents in such country covering licensed product, subject to earlier termination in the event of defaults by the parties under the license agreement.

License Agreement with Southern Research Institute

On December 22, 2004, we entered into an Option Agreement with the Southern Research Institute, or SRI, pursuant to which we were granted an exclusive option to obtain an exclusive license to SRI's interest in certain intellectual property, including exclusive rights related to certain isophosphoramidate mustard analogs. The Option Agreement was exercised on February 13, 2007. Under the license agreement entered into upon exercise of the option, we are required to remit minimum annual royalty payments of \$25 thousand until the first commercial sale of a licensed product. These payments were made for the years ended December 31, 2009, 2010 and 2011. We may be required to make payments upon achievement of certain milestones in varying amounts which on a cumulative basis could total up to \$775,000. In addition, SRI will be entitled to receive single digit percentage royalty payments on the sales of a licensed product in any country until all licensed patents rights in that country which are utilized in the product have expired. No milestones under the license agreement were reached or expensed during the years ended December 31, 2009, 2010 or 2011.

Also on December 22, 2004, we entered into a Research Agreement with SRI pursuant to which we agreed to spend a sum not to exceed \$200 thousand between the execution of the agreement and December 21, 2006, including a \$25

thousand payment that was made simultaneously with the execution of the agreement, to fund research and development work by SRI in the field of isophosphoramide mustard analogs.

TABLE OF CONTENTS

License Agreement with Baxter Healthcare Corporation

On November 3, 2006, we entered into a definitive Asset Purchase Agreement for indibulin and a License Agreement to proprietary nanosuspension technology with affiliates of Baxter Healthcare S.A. The purchase included the entire indibulin intellectual property portfolio as well as existing drug substance and capsule inventories. The terms of the Asset Purchase Agreement included an upfront cash payment of approximately \$1.1 million and an additional \$100 thousand payment for existing inventory, both of which were expensed in 2006. In addition to the upfront costs, the Asset Purchase Agreement includes additional diligence and milestone payments that could amount to approximately \$8.0 million in the aggregate and royalties on net sales of products covered by a valid claim of a patent for the life of the patent on a country-by-country basis. We expensed a \$625 thousand milestone payment upon the successful U.S. IND application for indibulin in 2007. The License Agreement requires payment of a \$15 thousand annual patent and license prosecution/maintenance fee through the expiration of the last of the licensed patents which is expected to expire in 2025, and single digit royalties on net sales of licensed products covered by a valid claim of a patent for the life of the patent on a country-by-country basis. The term of the license agreement extends until the expiration of the last to expire of the patents covering the licensed products, subject to earlier termination in the event of defaults by the parties under the license agreement.

In October 2009, the Baxter License Agreement was amended to allow us to manufacture indibulin. No milestones under the license agreement were reached or expensed during the years ended December 31, 2009, 2010 or 2011.

Exclusive Channel Partner Agreement with Intrexon Corporation

On January 6, 2011, we entered into an Exclusive Channel Partner Agreement, or the Channel Agreement, with Intrexon that governs a channel partnering arrangement in which we use Intrexon's technology directed towards *in vivo* expression of effectors in connection with the development of ZIN-CTI-001 and ZIN-ATI-001 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, which we collectively refer to as the Cancer Program. The Channel Agreement establishes committees comprised of representatives of us and Intrexon that govern activities related to the Cancer Program in the areas of project establishment, chemistry, manufacturing and controls, clinical and regulatory matters, commercialization efforts and intellectual property.

The Channel Agreement grants us a worldwide license to use patents and other intellectual property of Intrexon in connection with the research, development, use, importing, manufacture, sale, and offer for sale of products involving DNA administered to humans for expression of anti-cancer effectors for the purpose of treatment or prophylaxis of cancer, which we collectively refer to as the ZIOPHARM Products. Such license is exclusive with respect to any clinical development, selling, offering for sale or other commercialization of ZIOPHARM Products, and otherwise is non-exclusive. Subject to limited exceptions, we may not sublicense the rights described without Intrexon's written consent.

Under the Channel Agreement, and subject to certain exceptions, we are responsible for, among other things, the performance of the Cancer Program, including development, commercialization and certain aspects of manufacturing of ZIOPHARM Products. Intrexon is responsible for the costs of establishing manufacturing capabilities and facilities for the bulk manufacture of products developed under the Cancer Program, certain other aspects of manufacturing and costs of discovery-stage research with respect to platform improvements and costs of filing, prosecution and maintenance of Intrexon's patents.

Subject to certain expense allocations and other offsets provided in the Channel Agreement, we will pay Intrexon on a quarterly basis 50% of net profits derived in that quarter from the sale of ZIOPHARM Products, calculated on a ZIOPHARM Product-by-ZIOPHARM Product basis. We have likewise agreed to pay Intrexon on a quarterly basis 50% of revenue obtained in that quarter from a sublicensor in the event of a sublicensing arrangement. In addition, in partial consideration for each party's execution and delivery of the Channel Agreement, we entered into a Stock Purchase Agreement with Intrexon. (see Note 2)

TABLE OF CONTENTS

During the first 24 months of the agreement, either we or Intrexon may terminate the Channel Agreement in the event of a material breach by the other and Intrexon may terminate the Channel Agreement under certain circumstances if we assign our rights under the Channel Agreement without Intrexon's consent. Following the first 24 months of the agreement, Intrexon may also terminate the Channel Agreement if we fail to use diligent efforts to develop and commercialize ZIOPHARM Products or if we elect not to pursue the development of a Cancer Program identified by Intrexon that is a Superior Therapy as defined in the Channel Agreement. Also following the first 24 months of the agreement, we may voluntarily terminate the Channel Agreement upon 90 days written notice to Intrexon.

Upon termination of the Channel Agreement, we may continue to develop and commercialize any ZIOPHARM Product that, at the time of termination:

is being commercialized by us;
has received regulatory approval;
is a subject of an application for regulatory approval that is pending before the applicable regulatory authority; or
is the subject of at least an ongoing Phase 2 clinical trial (in the case of a termination by Intrexon due to an uncured breach or a voluntary termination by us), or an ongoing Phase 1 clinical trial in the field (in the case of a termination by us due to an uncured breach or a termination by Intrexon following an unconsented assignment by us or our election not to pursue development of a Superior Therapy).

Our obligation to pay 50% of net profits or revenue described above with respect to these retained products will survive termination of the Channel Agreement.

Collaboration Agreement with Harmon Hill, LLC

On April 8, 2008, we signed a Collaboration Agreement for Harmon Hill, LLC, or Harmon Hill, to provide consulting and other services for the development and commercialization of oncology therapeutics by us. Under the agreement we have agreed to pay Harmon Hill \$20 thousand per month for the consulting services and have further agreed to pay Harmon Hill (a) \$500 thousand upon the first patient dosing of the Specified Drug (as defined in the agreement) in a pivotal trial, which trial uses a dosing regimen introduced by Harmon Hill; and (b) provided that the Specified Drug receives regulatory approval from the FDA, the European Medicines Agency or another regulatory agency for the marketing of the Specified Drug, a 1% royalty of our net sales will be awarded to Harmon Hill. If the Specified Drug is sublicensed to a third party, the agreement entitles Harmon Hill to 1% award of royalties or other payments received from a sublicense. Subject to renewal or extension by the parties, the term of the agreement was for a one year period that expired April 8, 2009. Following such expiration, the parties continued to operate under the terms of the agreement and, during 2010, the agreement was formally extended through April 8, 2011 and again through April 8, 2012. We expensed \$240 thousand during each of the years ended December 31, 2009, 2010 and 2011 for consulting services per the aforementioned agreement. No milestones under the collaboration agreement were reached or expensed during the years ended December 31, 2009, 2010 or 2011.

Collaboration Agreement with Solasia Pharma K.K.

On March 7, 2011, we entered into a License and Collaboration Agreement with Solasia Pharma K.K., or Solasia.

Pursuant to the License and Collaboration Agreement, we granted Solasia an exclusive license to develop and commercialize darinaparsin in both IV and oral forms and related organic arsenic molecules, in all indications for human use in a pan-Asian/Pacific territory comprised of Japan, China, Hong Kong, Macau, Republic of Korea, Taiwan, Singapore, Australia, New Zealand, Malaysia, Indonesia, Philippines and Thailand.

TABLE OF CONTENTS

As consideration for the license, we received an upfront payment of \$5.0 million to be used exclusively for further clinical development of darinaparsin outside of the pan-Asian/Pacific territory, and will be entitled to receive additional payments of up to \$32.5 million in development-based milestones and up to \$53.5 million in sales-based milestones. We will also be entitled to receive double digit royalty payments from Solasia based upon net sales of licensed products in the applicable territories, once commercialized, and a percentage of sublicense revenues generated by Solasia.

The upfront payment for research and development funding is earned over the period of effort. We currently estimate this period to be 75 months, which could be adjusted in the future.

Under the License and Collaboration Agreement, we provide Solasia with drug product to conduct clinical trials. These transfers are accounted for as a reduction of research and development costs and an increase in collaboration receivables.

The agreement provides that Solasia will be responsible for the development and commercialization of darinaparsin in the pan-Asian/Pacific territory.

CRO Services Agreement with PPD Development, L. P.

We and PPD Development, L. P., or PPD, are parties to a Master Clinical Research Organization Services Agreement dated January 29, 2010, a related work order dated June 25, 2010 and a related work order dated April 8, 2011 under which PPD provides clinical research organization, or CRO, services in support of our clinical trials. PPD is entitled to cumulative payments of up to \$18.3 million under these arrangements, which is payable by us in varying amounts upon PPD achieving specified milestones. During the year ended December 31, 2010, we expensed \$1.8 million upon contract execution and \$1.1 million upon a clinical study commencement of enrollment in North America. During the year ended December 31, 2011, additional milestones related to commencing enrollment in Europe, Latin America and Asia along with enrollment based milestones were met and we recorded an aggregate \$4.0 million expense.

Patents and Other Intellectual Property Rights and Protection.

Patents extend for varying periods according to the date of patent filing or grant and the legal term of patents in the various countries where patent protection is obtained. The actual protection offering by a patent, which can vary from country to country, depends of the type of patent, the scope of its coverage and the availability of legal remedies in the country.

Pursuant to the Drug Price Competition and Patent Term Restoration Act of 1984, referred to as the Hatch-Waxman Amendments, some of our patents, under certain conditions, may be eligible for limited patent term extension for a period of up to five years as compensation for patent term lost during drug development and the FDA regulatory review process. However, this extension period cannot be extended beyond 14 years from the drug's approval date. The patent term restoration period is generally one-half the period of time elapsed between the effective date of an IND application or the issue date of the patent, whichever is later, and the submission date of an NDA, plus the period of time between the submission date of the NDA or the issue date of the patent, whichever is later, and FDA approval. The United States Patent and Trademark Office, in consultation with the FDA, reviews and approves applications for any patent term extension or restoration. We intend to seek the benefits of this statute, but there can be no assurance that we will be able to obtain any such benefits.

We also depend upon the skills, knowledge, and experience of our scientific and technical personnel, as well as those of our advisors, consultants, and other contractors, none of which is patentable. To help protect proprietary know-how, which is not patentable, and for inventions for which patents may be difficult to enforce, we currently rely, and in the future will continue to rely, on trade secret protection and confidentiality agreements to protect our interests. To this end, we generally require employees, consultants, advisors and other contractors to enter into confidentiality 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.

Our patent position and proprietary rights are subject to certain risks and uncertainties. Please read the Risk Factors section of this report for information about certain risks and uncertainties that may affect our patent position and proprietary rights.

TABLE OF CONTENTS

Additional information as of February 15, 2012 about material patents and other proprietary rights covering our product candidates is set forth below.

Palifosfamide

The patent estate covering palifosfamide compositions, methods of use, methods of manufacture, formulations, combination therapies and analogs includes three issued U.S. patents (two of which are scheduled to expire in 2029 and one of which is scheduled to expire in 2020), four pending U.S. patent applications, three issued foreign patents in Australia, New Zealand and South Africa and forty-nine pending foreign patent applications in Europe, Canada, Japan, Australia and fifteen other countries. Some of these patent assets are in-licensed from DEKK-Tec, Inc., some are in-licensed from Southern Research Institute, and some are owned by us.

ZIN-CTI-001 and ZIN-ATI-001

The patent estate licensed to us by Intrexon covering ZIN-CTI-001 and ZIN-ATI-001 compositions, methods of use, methods of manufacture, and formulations includes twenty-three issued U.S. patents (one of which is scheduled to expire in 2018, one of which is scheduled to expire in 2020, two of which are scheduled to expire in 2021, six of which are scheduled to expire in 2022, three of which are scheduled to expire in 2023, three of which are scheduled to expire in 2024, three of which are scheduled to expire in 2025, three of which are scheduled to expire in 2026, and one of which is scheduled to expire in 2029), forty-two pending U.S. patent applications, one-hundred-seventeen issued foreign patents in Europe, Canada, Japan, Australia and nine other countries, and two-hundred-forty-nine pending foreign patent applications in Europe, Canada, Japan, Australia and thirteen other countries.

Indibulin

The patent estate covering indibulin compositions, methods of use, methods of manufacture, formulations and combination therapies includes seven issued U.S. patents (three of which are scheduled to expire in 2017 and four of which are scheduled to expire in 2019), three pending U.S., patent applications, one PCT (Patent Cooperation Treaty) patent application, one-hundred-thirty-nine issued foreign patents in Europe, Canada, Japan, Australia and sixteen other countries, and thirty-seven pending foreign patent applications in Europe, Canada, Japan, Australia and nine other countries. Some of these patent assets are in-licensed from affiliates of Baxter Healthcare Corporation and some of which are owned by us.

Darinaparsin

The patent estate covering darinaparsin compositions, methods of use, methods of manufacture, formulations, polymorphic forms, analogs and combination therapies includes five issued U.S. patents (three of which are scheduled to expire in 2023, one of which is scheduled to expire in 2025 and one of which is scheduled to expire in 2026), seven pending U.S. patent applications, six issued foreign patents in Australia, Japan, Israel and Singapore and sixty-three pending foreign patent applications in Europe, Canada, Japan, Australia and thirteen other countries. Some of these patent assets are in-licensed from The University of Texas M. D. Anderson Cancer Center and the Texas A&M University System and some are owned by us.

Governmental Regulation

The research, development, testing, manufacture, labeling, promotion, advertising, distribution, and marketing, among other things, of our products are extensively regulated by governmental authorities in the United States and other

countries. In the United States, the FDA regulates drugs under the Federal Food, Drug, and Cosmetic Act, or the FDCA, and its implementing regulations. Failure to comply with the applicable U.S. requirements may subject us to administrative or judicial sanctions, such as FDA refusal to approve pending NDAs, warning letters, product recalls, product seizures, total or partial suspension of production or distribution, injunctions, and/or criminal prosecution.

Drug Approval Process. None of our drugs may be marketed in the United States until the drug has received FDA approval. The steps required before a drug may be marketed in the United States include:

Preclinical laboratory tests, animal studies, and formulation studies;
Submission to the FDA of an IND for human clinical testing, which must become effective before human clinical trials may begin;

13

TABLE OF CONTENTS

Adequate and well-controlled human clinical trials to establish the safety and efficacy of the drug for each indication;
Submission to the FDA of NDA or biologic license application, or BLA;
Satisfactory completion of an FDA inspection of the manufacturing facility or facilities at which the drug is produced to assess compliance with current good manufacturing practices, or cGMPs; and
FDA review and approval of the NDA or BLA.

Preclinical tests include laboratory evaluation of product chemistry, toxicity, and formulation, as well as animal studies. The conduct of the preclinical tests and formulation of the compounds for testing must comply with federal regulations and requirements. The results of the preclinical tests, together with manufacturing information and analytical data, are submitted to the FDA as part of an IND application, which must become effective before human clinical trials may begin. An IND automatically takes effect 30 calendar days after receipt by the FDA, unless before that time the FDA raises safety concerns or questions about issues such as the design of the trials as outlined in the IND. In such a case, the IND sponsor and the FDA must resolve any outstanding FDA concerns or questions before clinical trials may proceed. We cannot be certain that submission of an IND will result in the FDA allowing a clinical trial to be initiated.

Clinical trials involve the administration of an investigational drug to human subjects under the supervision of qualified investigators. Clinical trials are conducted according to protocols that detail the study objectives, the parameters to be used in monitoring participants' safety, and the effectiveness criteria by which the investigational drug will be evaluated. Each protocol must be submitted to the FDA as part of the IND.

Clinical trials are typically conducted in three sequential phases, but the phases may overlap. The study protocol and informed consent information for study subjects in a clinical trial must also be approved by an Institutional Review Board for each institution where the trial will be conducted. Study subjects must sign an informed consent form before participating in a clinical trial. Phase 1 usually involves the initial introduction of the investigational drug into people to evaluate its short-term safety, dosage tolerance, metabolism, pharmacokinetics, and pharmacologic actions and, if possible, to gain an early indication of its effectiveness. Phase 2 usually involves trials in a limited patient population in order to (1) evaluate dosage tolerance and appropriate dosage; (2) identify possible adverse effects and safety risks; and (3) evaluate preliminarily the efficacy of the drug for specific indications. Phase 3 trials usually continue to evaluate clinical efficacy and further test for safety by using the drug in its final form in an expanded patient population. There can be no assurance that Phase 1, Phase 2, or Phase 3 testing will be completed successfully within any specified period of time, if at all. Furthermore, the sponsoring company or the FDA may suspend clinical trials at any time on various grounds, including a finding that the subjects or patients are being exposed to an unacceptable health risk.

The FDCA permits the FDA and the IND sponsor to agree in writing on the design and size of clinical studies intended to form the primary basis of a claim of effectiveness in an NDA application. This process is known as Special Protocol Assessment, or SPA, and can be a somewhat lengthy process. An agreement may not be changed by the sponsor or FDA after the trial begins, except (1) with the written agreement of the sponsor and the FDA, or (2) if the director of the FDA reviewing division determines that a substantial scientific issue essential to determining the safety or effectiveness of the drug was identified after the testing began.

Assuming successful completion of the required clinical testing, the results of the preclinical studies and of the clinical studies, together with other detailed information, including information on the manufacture and composition of the drug, are submitted to the FDA in the form of an NDA requesting approval to market the product for one or more indications. The testing and approval process requires substantial time, effort, and financial resources. The FDA reviews the application and may deem it to be inadequate to support the registration, and companies cannot be sure that any approval will be granted on a timely basis, if at all. The FDA may also refer the application to the appropriate advisory committee, typically a panel of clinicians, for review, evaluation and a recommendation as to whether the

application should be approved. The FDA is not bound by the recommendations of the advisory committee.

TABLE OF CONTENTS

The NDA or BLA application is the vehicle through which investigational drug sponsors formally propose that the FDA approve a new pharmaceutical agent to be marketed and sold in the U.S. The data gathered during the animal studies and human clinical trials of an IND become part of the NDA or BLA.

The goals of the NDA/BLA are to provide enough information to permit FDA to reach the following key decisions:

Is the drug safe and effective in its proposed use(s), and do the benefits of the drug outweigh the risks?

Is the drug's proposed labeling (package insert) appropriate, and what it should contain?

Are the methods used in manufacturing the drug and the controls used to maintain the drug's quality adequate to preserve the drug's identity, strength, quality, and purity?

The FDA has various programs, including Exploratory INDs (also referred to as Phase 0), orphan drug, fast track, priority review, and accelerated approval, which are intended to expedite or simplify the process for developing and reviewing drugs, and/or provide for approval on the basis surrogate endpoints, or provide financial incentives and market exclusivity. Generally, drugs that may be eligible for one or more of these programs are those for serious or life-threatening conditions, those with the potential to address unmet medical needs, and those that provide meaningful benefit over existing treatments. A company cannot be certain that any of its investigational drugs will qualify for any of these programs, or that, if a drug does qualify, the review time will be reduced.

Section 505(b)(2) of the FDCA allows the FDA to approve a follow-on drug on the basis of data in the scientific literature or a prior FDA approval of an NDA for a related drug. Specifically, a 505(b)(2) application is one for which one or more of the investigations relied upon by the applicant for approval were not conducted by or for the applicant, and for which the applicant has not obtained a right of reference or use from the person by or for whom the investigations were conducted. A 505(b)(2) application may be submitted for a new drug product when some part of the data necessary for approval are derived from studies not conducted by or for the applicant and to which the applicant has not obtained a right of reference. For a new drug, these data are likely to be derived from published studies rather than the FDA's previous finding of safety and effectiveness of a drug. For changes to a previously approved drug product, an application may rely on the FDA's finding of safety and effectiveness of the previously approved product, coupled with the information needed to support the change from the approved product. The additional information could be new studies conducted by the applicant or published data. This use of Section 505(b)(2), described in the regulations at 21 CFR 314.54, was intended to encourage innovation without creating duplicate work, and reflects the principle that it is wasteful and unnecessary to carry out studies to demonstrate what is already known about a drug. This procedure potentially makes it easier for generic drug manufacturers to obtain rapid approval of new forms of drugs based on proprietary data of the original drug manufacturer.

Before approving an NDA or BLA, the FDA usually will inspect the facility or the facilities at which the drug is manufactured and will not approve the product unless cGMP compliance is satisfactory. If the FDA evaluates the NDA or BLA and the manufacturing facilities and deems them to be acceptable, the FDA may issue an approval letter, or in many cases, a complete response letter followed subsequently by an approval letter. The complete response letter contains the conditions that must be met in order to secure final approval of the NDA or BLA. When and if those conditions have met with the FDA's satisfaction, the FDA will issue an approval letter. The approval letter authorizes commercial marketing of the drug for specific indications. As a condition of NDA/BLA approval, the FDA may require post-marketing testing and surveillance to monitor the drug's safety or efficacy, or impose other conditions.

After approval, certain changes to the approved drug product, such as adding new indications, initiating certain manufacturing changes, or making certain additional labeling claims, are subject to further FDA review and approval. Before a company can market a drug product for any additional indication(s), it must obtain additional approval from FDA. Obtaining approval for a new indication generally requires that additional clinical studies be conducted. A

company cannot be sure that any additional approval for new indications for any product candidate will be approved on a timely basis, or at all.

15

TABLE OF CONTENTS

Post-approval Requirements. Often times, even after a drug has been approved by the FDA for sale, the FDA may require that certain post-approval requirements be satisfied, including the conduct of additional clinical studies. If such post-approval conditions are not satisfied, the FDA may withdraw its approval of the drug. In addition, holders of an approved NDA are required to: (1) report certain adverse reactions to the FDA; (2) comply with certain requirements concerning advertising and promotional labeling for their products; and (3) continue to have quality control and manufacturing procedures conform to cGMP. The FDA periodically inspects the sponsor's records relating to safety reporting and/or manufacturing facilities; this latter effort includes assessment of cGMP compliance. Accordingly, manufacturers must continue to expend time, money, and effort in the area of production and quality control to maintain cGMP compliance. We intend to use third-party manufacturers to produce our products in clinical and commercial quantities, and future FDA inspections may identify compliance issues at the facilities of our contract manufacturers that may disrupt production or distribution, or require substantial resources to correct. In addition, discovery of problems with a product after approval may result in restrictions on a product, manufacturer, or holder of an approved NDA, including withdrawal of the product from the market.

Patent Challenge Process Regarding ANDAs. The Hatch-Waxman Act provides incentives for generic pharmaceutical manufacturers to challenge patents on branded pharmaceutical products and/or their methods of use, as well as to develop products comprising non-infringing forms of the patented drugs. The Hatch-Waxman legislation places significant burdens on the Abbreviated New Drug Application, or ANDA, filer to ensure that such challenges are not frivolous, but also offers the opportunity for significant financial reward if the challenge is successful.

If there is a patent listed for the branded drug in the FDA's Orange Book at the time of submission of the ANDA or at any time before the ANDA is approved and the generic company intends to market the generic equivalent prior to the expiration of that patent, the generic company includes a certification asserting that the patent is invalid, unenforceable and/or not infringed, a so-called paragraph IV certification.

After receiving notice from the FDA that its application is acceptable for review or immediately if the ANDA has been amended to include a paragraph IV certification after the application was submitted to the FDA, the company filing a generic application is required to send the patent holder and the holder of the NDA for the brand-name drug a notice explaining why it believes that the patents in question are invalid, unenforceable or not infringed. Upon receipt of the notice from the generic applicant, the patent holder has 45 days during which to bring a patent infringement suit in federal district court against the generic applicant in order to obtain the 30 month automatic stay.

If a suit is commenced by the patent holder during the 45-day period, the Hatch-Waxman Act provides for an automatic stay on the FDA's ability to grant final approval of the ANDA for the generic product. Patent holders may only obtain one 30 month stay with respect to patents that were listed at the time an ANDA was filed. The period during which the FDA may not approve the ANDA and the patent challenger therefore may not market the generic product is 30 months, or such other period as may be ordered by the court. The 30-month period may or may not, and often does not, coincide with the timing of the resolution of the lawsuit or the expiration of a patent, but if the patent challenge is successful or the challenged patent expires during the 30-month period, the FDA may approve the generic drug for marketing, assuming there are no other obstacles to approval such as periods of non-patent exclusivity given to the NDA holder.

Under the Hatch-Waxman Act, any developer of a generic drug that is considered first to have filed its ANDA for review by the FDA, and whose filing includes a paragraph IV certification, may be eligible to receive a 180-day period of generic market exclusivity. This period of market exclusivity may provide the patent challenger with the opportunity to earn a return on the risks taken and its legal and development costs and to build its market share before other generic competitors can enter the market. If the ANDA of the first applicant accepted for filing is withdrawn, the 180-day exclusivity period is forfeited and unavailable to any other applicant.

TABLE OF CONTENTS

Employees

As of February 15, 2012, we had 66 employees.

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. Following reincorporation in Delaware in May 2005 under the same name, we completed a reverse acquisition of privately held ZIOPHARM, Inc., a Delaware corporation on September 13, 2005. 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, or 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, 20th 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 report, unless expressly noted.

Available Information

Our website address is *www.ziopharm.com*. Information contained on our website is not incorporated by reference into this report unless expressly noted. We file reports with the SEC, which we make available on our website free of charge. These reports include annual reports on Form 10-K, quarterly reports on Form 10-Q, current reports on Form 8-K and amendments to such reports, each of which is provided on our website as soon as reasonably practicable after we electronically file such materials with or furnish them to the SEC. You can also read and copy any materials we file with the SEC at the SEC's Public Reference Room at 100 F Street, N.E., Washington, DC 20549. You can obtain additional information about the operation of the Public Reference Room by calling the SEC at 1-800-SEC-0330. In addition, the SEC maintains a website (*www.sec.gov*) that contains reports, proxy and information statements, and other information regarding issuers that file electronically with the SEC, including us.

TABLE OF CONTENTS

Item 1A. Risk Factors

An investment in our common stock is very risky. In addition to the other information in this annual report on Form 10-K, you should consider carefully the following risk factors in evaluating us and our business. If any of the events described in the following risk factors were to occur, our business, financial condition, results of operation and future growth prospects would likely be materially and adversely affected. In that event, the trading price of our common stock could decline and you could lose all or a part of your investment in our common stock.

Therefore, we urge you to carefully review this entire report and consider the risk factors discussed below. Moreover, the risks described below 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, financial condition, operating results or prospects.

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 not generated significant revenue and have incurred significant net losses in each year since our inception.

For the year ended December 31, 2011, we had a net loss of \$63.8 million, and, as of December 31, 2011, we have incurred approximately \$187.6 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 may develop under our channel partnering arrangement with Intrexon, will likely require substantial increases in our expenses as we:

- Continue to undertake clinical trials for product candidates;
- Scale-up the formulation and manufacturing of our product candidates;
- Seek regulatory approvals for product candidates;
- 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 candidates. 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 and to synthetic biology, further progress with the development of our other candidates may be significantly delayed and may depend on the success of our ongoing clinical trial involving palifosfamide.

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 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 December 31, 2011, we had incurred approximately \$187.6 million of cumulative net losses and had approximately \$104.7 million of cash and cash equivalents. Taking into account our receipt of approximately \$49.1 million in net proceeds from our January 2012 public offering of common stock, and given our current plans for development of our product candidates, we anticipate that our cash resources will

TABLE OF CONTENTS

be sufficient to fund our operations into the second half of 2013. However, changes may occur that would consume our existing capital prior to that time, including expansion of the scope, and/or slower than expected 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. 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 current timing expectations to complete enrollment in the study by the end of the first quarter of 2012. We have also assumed responsibility for the advancement of two product candidates in the clinic under our exclusive channel partnership with Intrexon and we expect that the costs associated with these and 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 assumed development responsibility for these products on January 6, 2011 and the actual costs associated therewith may be significantly in excess of forecasted amounts.

In addition to above 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. 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, 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 to existing stockholders 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:

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

Unforeseen safety issues;
Determination of dosing issues;
Lack of effectiveness during clinical trials;
Slower than expected rates of patient recruitment and enrollment;

TABLE OF CONTENTS

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 in a small number of sites in the United States as we pursued site review board clearance for trial conduct in the anticipated 150 or more sites expected worldwide. Site opening is a complex and time-consuming process, often requiring six months to complete outside of the United States. PICASSO 3 has a targeted enrollment of 424 patients. We experienced slower than anticipated enrollment in the trial at start-up due in part to the timing of site openings and regulatory approvals.

While enrollment is complicated by a number of factors outside of our control, we currently expect that full enrollment will occur by the end of the first quarter of 2012. The outcome in progression-free survival, the study's primary endpoint for accelerated approval, is anticipated late in the second half of 2012 should the trial complete enrollment as expected. However, we cannot assure that we will be able to enroll the sufficient number of patients in the PICASSO 3 trial to meet our expectation for full enrollment or that our projections for progression will occur. As an orphan designated indication, the patient population available for participation in the PICASSO 3 trial is generally limited. If we cannot meet our forecasted enrollment, 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 for treatment of soft tissue sarcomas and darinaparsin for treatment of peripheral T-cell lymphoma in both the United States and 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 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 United States 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.

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 drug 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 drugs 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.

TABLE OF CONTENTS

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

Our exclusive channel partnership with Intrexon 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 biotherapeutics, with ZIN-CTI-001 currently in a Phase 1b study and the FDA having accepted an IND application to begin clinical study of ZIN-ATI-001 in oncology. 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 herein that apply to our small molecule drug candidates, which are in various stages of development, also apply to product candidates that we seek to develop under our exclusive channel partnership with Intrexon.

We will incur additional expenses in connection with our exclusive channel partnering arrangement with Intrexon Corporation.

The *in vivo* effector platform, in which we have acquired rights for cancer from Intrexon, includes two existing product candidates, with DC-RTS-IL-12 and Ad-RTS-IL-12 both currently in Phase 1 study. 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 due to complexity, 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, and continue to add, headcount in part to support our exclusive channel partnership endeavors, 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 assumed development responsibility for these products on January 6, 2011 and the actual costs associated therewith may be significantly in excess of forecasted 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 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;

The technology on which our channel partnering arrangement with Intrexon Corporation is based in part on early stage

Participating in regulatory approval process;
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.

TABLE OF CONTENTS

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 and technology.

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.

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.

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,

Because we currently neither have nor intend to establish internal research capabilities, we are dependent upon ph

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.

TABLE OF CONTENTS

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, Richard Bagley, our President, Chief Operating Officer and Chief Financial Officer, Dr. Hagop Youssoufian, our President of Research & Development and Chief Medical Officer, Caesar J. Belbel, our Executive Vice President and Chief Legal Officer, and our principal scientific, regulatory, and medical advisors. Dr. Lewis, Mr. Bagley, Dr. Youssoufian and Mr. Belbel's employment are governed by written employment agreements. The employment agreements with Dr. Lewis and Mr. Bagley provide for terms that expire in January 2013 and June 2013, respectively. Drs. Lewis and Youssoufian, and Messrs. Bagley and Belbel 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 Drs. Lewis and Youssoufian and Messrs. Bagley and Belbel, 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 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, an 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.

We rely on key executive officers and scientific and medical advisors, and their knowledge of our business and technical

TABLE OF CONTENTS

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 United States 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 an NDA or 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.

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. 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 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.

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 or BLA for regulatory approval of our product candidates or whether such an NDA or BLA will be accepted. Because we do not anticipate generating revenues unless and until we submit one or more NDAs or BLAs and thereafter obtain requisite FDA approvals, the timing of our NDA or BLA submissions and FDA determinations regarding approval thereof, will directly affect if and when we are able to generate revenues.

TABLE OF CONTENTS

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. The 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 metastatic 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.

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.

25

TABLE OF CONTENTS

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 TO 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 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.

TABLE OF CONTENTS

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 drugs;

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 drugs 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:

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.

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.

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

TABLE OF CONTENTS

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.

Our ability to use net operating loss carryforwards to reduce future tax payments may be limited or restricted.

We have generated significant net operating loss carryforwards, or NOLs, as a result of our incurrence of losses since inception. We generally are able to carry NOLs forward to reduce taxable income in future years. However, our ability to utilize the NOLs is subject to the rules of Section 382 of the Internal Revenue Code. Section 382 generally restricts the use of NOLs after an ownership change. An ownership change occurs if, among other things, the stockholders (or specified groups of stockholders) who own or have owned, directly or indirectly, 5% or more of a corporation's common stock or are otherwise treated as 5% stockholders under Section 382 and the U.S. Treasury Department regulations promulgated thereunder increase their aggregate percentage ownership of that corporation's stock by more than 50 percentage points over the lowest percentage of the stock owned by these stockholders over a three-year rolling period. In the event of an ownership change, Section 382 imposes an annual limitation on the amount of taxable income a corporation may offset with NOL carry forwards. This annual limitation is generally equal to the product of the value of the corporation's stock on the date of the ownership change, multiplied by the long-term tax-exempt rate published monthly by the Internal Revenue Service. Any unused annual limitation may be carried over to later years until the applicable expiration date for the respective NOL carry forwards. We may have experienced an ownership change within the meaning of Section 382 in the past. As a result, our NOLs may be subject to limitations and we may be required to pay taxes earlier and in larger amounts than would be the case if our NOLs were freely usable.

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 and with respect to the Intrexon technology, including the existing Intrexon product candidates.

Under our Channel Agreement with Intrexon, Intrexon has the sole right to conduct and control the filings, prosecution and maintenance of the patents and patent applications licensed to us. Although under the agreement Intrexon has agreed to consider in good faith and consult with us regarding any comments we may have regarding these 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 United States 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;

28

TABLE OF CONTENTS

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.

Changes in patent laws or in interpretations of patent laws in the United States and other countries may diminish the value of our intellectual property or narrow the scope of our patent protection. In September 2011, the Leahy-Smith Invents Act, or the Leahy-Smith Act, was signed into law, resulting in a number of significant changes to U.S. patent law. These changes include provisions that affect the way patent applications will be prosecuted and may also affect patent litigation. In addition, the U.S. Supreme Court has ruled on several patent cases in recent years, either narrowing the scope of patent protection available in certain circumstances or weakening the rights of patent owners in certain situations. This combination of events has created uncertainty with respect to the value of patents, once obtained, and with regard to our ability to obtain patents in the future. Depending on decisions by the U.S. Patent and Trademark Office, which is developing regulations and procedures to implement the Leahy-Smith Act, and federal courts, the laws and regulations governing patents could change in unpredictable ways that would weaken our ability to obtain new patents or to enforce our existing patents and patents that we might obtain in the future.

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 patents on technologies, compositions and methods of use that are related to our business and may cover or conflict with our owned or licensed 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 rejection of claims in our patent applications. Because patent applications in the United States and many foreign jurisdictions are typically not published until eighteen months after filing, or in some cases not at all, and because publications of discoveries in the scientific literature often lag behind actual discoveries, neither we nor our licensors can be certain that others have not filed or maintained patent applications for technology used by us or covered by our pending patent applications without our being aware of these 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 rejection of claims in 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 owned or licensed 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 infringement litigation against third parties. Similarly, we may be sued by others for patent infringement. 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

TABLE OF CONTENTS

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.

Our research, development and commercialization activities, as well as any product candidates or products resulting from these activities, may infringe or be claimed to infringe patents or patent applications under which we do not hold licenses or other rights. Patents do not protect its owner from a claim of infringement of another owner's patent. Therefore, our patent position cannot and does not provide any assurance that we are not infringing the patent rights of another.

The patent landscape in the field of novel DNA biotherapeutics, which we are pursuing under our exclusive channel partnership with Intrexon, is particularly complex. We are aware of numerous U.S. and foreign patents and pending patent applications of third parties that cover compositions, methods of use and methods of manufacture of novel DNA biotherapeutics, including biotherapeutics involving the *in vivo* expression of human IL-12. In addition, there may be patents and patent applications in the field of which we are not aware. The technology we license from Intrexon is early-stage technology and we are just beginning the process of designing and developing products using this technology. Although we will seek to avoid pursuing the development of products that may infringe any patent claims that we believe to be valid and enforceable, we may fail to do so. Moreover, given the breadth and number of claims in patents and pending patent applications in the field of novel DNA biotherapeutics and the complexities and uncertainties associated with them, third parties may allege that we are infringing upon patent claims even if we do not believe such claims to be valid and enforceable.

If a claim for patent infringement 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.

If we breach any of the agreements under which we license rights to products or technology from others, we could lose license rights that are material to our business or be subject to claims by our licensors.

We license rights to products and technology that are important to our business, and we expect to enter into additional licenses in the future. For instance, we have exclusively licensed patents and patent applications under our agreement with Intrexon. Under these agreements, we are subject to a range of commercialization and development, sublicensing, royalty, patent prosecution and maintenance, insurance and other obligations.

Any failure by us to comply with any of these obligations or any other breach by us of our license agreements could give the licensor the right to terminate the license in whole, terminate the exclusive nature of the license or bring a

If we breach any of the agreements under which we license rights to products or technology from others, we could

claim against us for damages. Any such termination or claim could have a material adverse effect on our financial condition, results of operations, liquidity or business. Even if we contest any such termination or claim and are ultimately successful, such dispute could lead to delays in the development or commercialization of potential products and result in time-consuming and expensive litigation or arbitration. On termination we may be required to license to the licensor any related intellectual property that we developed.

In addition, in certain cases, the rights licensed to us are rights of a third party licensed to our licensor. In such instances, if our licensors do not comply with their obligations under such licenses, our rights under our license agreements with our licensor may be adversely affected.

TABLE OF CONTENTS

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, or the Exchange Act, and other federal securities laws. As a result, we incur significant legal, accounting, and other expenses that we would 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 financial 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. 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. As a company with limited accounting resources, a significant amount of management's time and attention has been and will continue to be diverted from our business to ensure compliance with these regulatory requirements. This diversion of management's time and attention may have a material adverse effect on our business, financial condition and results of operations.

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 identified in our internal control over financial reporting that we cannot remediate in a timely manner, or if we are unable to receive a positive attestation from our independent registered public accounting firm with respect to our internal controls over financial reporting, 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 SEC. 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, Section 203 of the Delaware General Corporation Law generally 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 2011 issuance of shares of common stock to Intrexon in a private placement transaction, our board of directors waived the Section 203 prohibition with respect to a future business combination with Intrexon. 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.

TABLE OF CONTENTS

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 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 us will be realized, if at all, only when you sell shares of our common stock.

Item 1B. Unresolved Staff Comments

None.

Item 2. Properties

Our corporate office is located at 1180 Avenue of the Americas, 20th Floor, New York, NY 10036. The New York office space is subject to a lease agreement that expires in August 2018. Under the terms of the lease, we lease approximately six thousand square feet and are required to make rental payments at an average monthly rate of approximately \$34 thousand through the remainder of the term of the lease. We also maintain business and development operations in Boston, MA in an office facility that occupies approximately twenty-one thousand square feet. The Boston office space consists of three floors which are leased pursuant to a lease agreement that expires August 2016 under which we are required to make rental payments at an average monthly rate of approximately \$48 thousand through the remainder of the lease term. We also maintain business operations in Germantown, MD. The Maryland office space is subject to a lease agreement that expires in March 2014. Under the terms of the lease, we lease approximately two thousand square feet and are required to make rental payments at an average monthly rate of approximately \$4 thousand through the remainder of the lease. (see Note 8 to the financial statements, Commitments and Contingencies).

Item 3. Legal Proceedings

In the ordinary course of business, we may periodically become subject to legal proceedings and claims arising in connection with ongoing business activities. The results of litigation and claims cannot be predicted with certainty, and unfavorable resolutions are possible and could materially affect our results of operations, cash flows or financial position. In addition, regardless of the outcome, litigation could have an adverse impact on us because of defense costs, diversion of management resources and other factors.

While the outcome of these proceedings and claims cannot be predicted with certainty, there are no matters, as of December 31, 2011, that, in the opinion of management, might have a material adverse effect on our financial position, results of operations or cash flows.

Item. 4. Mine Safety Disclosures

Not applicable.

TABLE OF CONTENTS**PART II****Item 5. Market for Common Equity and related Stockholders Matters****Market for Common Stock**

Our common stock trades on the NASDAQ Capital Market under the symbol ZIOP. The following table sets forth the high and low sale prices for our common stock during each quarter within the two most recently completed fiscal years as reported by the NASDAQ Capital Market.

Quarter Ended	2011		2010	
	High	Low	High	Low
March 31	\$ 6.25	\$ 4.72	\$ 5.09	\$ 2.91
June 30	\$ 7.70	\$ 5.88	\$ 6.09	\$ 3.18
September 30	\$ 6.07	\$ 4.41	\$ 4.02	\$ 3.14
December 31	\$ 5.20	\$ 3.85	\$ 5.05	\$ 3.71

Record Holders

As of February 15, 2012, we had approximately 153 holders of record of our common stock, one of which was Cede & Co., a nominee for Depository Trust Company, or DTC. Shares of common stock that are held by financial institutions as nominees for beneficial owners are deposited into participant accounts at DTC, and are considered to be held of record by Cede & Co. as one stockholder. As of February 15, 2012, we had approximately 8,794 beneficial holders of our common stock.

Dividends

We have never declared or paid a cash dividend on our common stock and do not anticipate paying any cash dividends in the foreseeable future.

Recent Sales of Unregistered Securities

None.

Issuer Purchases of Equity Securities

During the three months ended December 31, 2011, we purchased 44,369 shares of restricted stock from employees to cover withholding taxes due from the employees at the time that applicable forfeiture restrictions lapsed. The following table provides information about these purchases of restricted shares for the three months ended December 31, 2011:

Period	Total Number of Shares Purchased	Average Price Paid Per Share (\$)
October 1 to 31, 2011		\$
November 1 to 30, 2011		\$
December 1 to 31, 2011	44,369	\$ 4.41
Total	44,369	

Stockholder Return Comparison

The information included in this section is not deemed to be soliciting material or to be filed with the SEC or subject to Regulation 14A or 14C under the Exchange Act or to the liabilities of Section 18 of the Exchange Act, and will not be deemed to be incorporated by reference into any filing under the Securities Act or the Exchange Act, except to the extent we specifically incorporate it by reference into such a filing.

The graph below matches the cumulative 5-year total return of holders of our common stock with the cumulative total returns of the NASDAQ Composite index and the NASDAQ Biotechnology index. The graph assumes that the value of the investment in our common stock and in each of the indexes (including reinvestment of dividends) was \$100 on December 31, 2006 and tracks it through December 30, 2011.

TABLE OF CONTENTS

**Comparison of 5 Year Cumulative Total Return
Assumes Initial Investment of \$100
December 2011**

Item 6. Selected Financial Data

The selected financial data presented below has been derived from our financial statements. This data may not be indicative of our future financial condition or results of operations and should be read in conjunction with Management's Discussion and Analysis of Financial Condition and Results of Operations and our financial statements and accompanying notes included elsewhere herein.

	Year Ended December 31,				
	2011	2010	2009	2008	2007
	(in thousands, except per share amounts)				
Statements of Operations Data:					
Research contract revenue	\$ 667	\$	\$	\$	\$
Total operating expenses	72,067	24,546	12,123	25,619	28,570
Loss from operations	(71,400)				