ZIOPHARM ONCOLOGY INC
Form 10-K
March 18, 2013
Table of Contents

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, 2012

OR

¨ **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)

Delaware	84-1475642
(State or Other Jurisdiction of Incorporation or Organization)	(IRS Employer Identification No.)
1180 Avenue of the Americas, 20th Floor, New York, NY	10036
(Address of Principal Executive Offices)	(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 x

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 x

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 x 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 x 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, accelerate filer and smaller reporting company in Rule 12b-2 of the Exchange Act. (Check one):

Large Accelerated Filer ¨	Accelerated Filer x
Non-Accelerated Filer ¨	Smaller Reporting Company ¨

Indicate by check mark whether the registrant is a shell company (as defined in Rule 12b-2 of the Act). Yes ¨ No x

The aggregate market value of the registrant s common stock held by non-affiliates was $396,154,064 as of June 30, 2012 (the last business day of the registrant s most recently completed second fiscal quarter), based on a total of 66,580,515 shares of common stock held by non-affiliates and on a closing price of $5.95 as reported on the NASDAQ Capital Market on June 30, 2012.

As of February 22, 2013, there were 83,703,934 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 2013 annual meeting of stockholders, which is to be filed within 120 days after the end of the fiscal year ended December 31, 2012, 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, 2012

TABLE OF CONTENTS

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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 through the licensing and development of proprietary small molecule drug candidates and a synthetic biology platform. Our small molecule drug candidates 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 small molecule clinical programs include palifosfamide (ZIO-201), indibulin (ZIO-301) and darinaparsin (ZIO-101). We are also pursuing the development of our synthetic biology platform 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 stimulate key pathways used by the body s immune system to inhibit the growth and metastasis of cancers, adding significantly to our small molecule drug development portfolio and utilizing our capabilities to translate science to the patient setting.

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. Our lead palifosfamide program, PICASSO 3, a global pivotal Phase 3 trial to support registration in combination with doxorubicin in the first-line setting of metastatic soft tissue sarcoma, or STS completed enrollment in June 2012. The results of our PICASSO 3 pivotal trial in first-line STS are expected in the last week of March 2013. Enrollment is ongoing in a global pivotal Phase 3 trial to support registration in combination with platinum and etoposide in the treatment of metastatic small cell lung cancer (SCLC).

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 was estimated that about 1,660,290 new cases of cancer are expected to be diagnosed in 2013 and about 580,350 Americans are expected to die from cancer in 2013 more

Table of Contents

than 1,600 each day. The cost of treating cancer is significant. The National Institute of Health estimates that the overall costs of cancer in 2008 were $201.5 billion. These costs included an estimate of $77.4 billion in direct medical costs and $124.0 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 treatment of cancer is supportive care; and recently, immunological-based approaches have shown 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 used 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.

Table of Contents

Product Candidates

Palifosfamide, ZIO-201

General. Palifosfamide, or isophosphoramide mustard, referred to as 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 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 without the acrolein or chloroacetaldehyde metabolites we believe that the administration of palifosfamide may be a more effective and well 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, or 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 STS 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. Doxorubicin, approved decades ago, is the only FDA-approved treatment for first-line metastatic sarcoma with Votrient® now approved for second-line. 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, or 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.

Table of Contents

Other Indications. Palifosfamide may be useful to treat many other solid tumors, including pediatric cancer, and hematological malignancies. Oral palifosfamide could also offer not only a significant advancement to current therapies but also greater patient access and convenience.

STS and SCLC, Significant Unmet Medical Need. Both first-line metastatic STS and metastatic 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, initial care is usually 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 is either first diagnosed in the advanced setting or has re-occurred and surgery is no longer an option. Chemotherapy is the standard of care for first-line metastatic STS and doxorubicin is the only first-line therapy approved in the United States for its treatment. We believe the annual projection in the United States for first-line metastatic STS treatment is approximately 9,000 patients. While data sources for Europe are limited, we estimate, based on epidemiology, an annual projection in Europe for first-line metastatic STS treatment of approximately 14,000 patients, for a combined U.S. and European estimate of 23,000 patients annually. For SCLC, the estimated U.S. annual incidence is 30,000 35,000 patients and 250,000 patients worldwide. Approximately 70% of patients have metastatic disease. Platinum and etoposide are standard of care in the first-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. 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 STS. We reported favorable results and safety profile from this study at the 2009 annual meeting of the American Society of Clinical Oncology, or ASCO. 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 first- 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 the Data Committee, sarcoma experts, and our Medical Advisory Board, we elected to suspend enrollment in the trial in October 2009. We subsequently presented further positive interim data from the trial at the 15th Annual Connective Tissue Oncology Society meeting held in November 2009 and again at the 2010 ASCO annual meeting in June 2010, where the presentation was selected for Best of ASCO. As presented at ASCO, the Phase 2 PICASSO trial randomized a total of 67 patients with 66 treated and 62 eligible for evaluation. The study was powered to show a difference in progression-free survival, or PFS, between doxorubicin in combination with palifosfamide versus doxorubicin alone. An analysis of the evaluable data reported a hazard ratio of 0.43 (p=0.019). Safety data were similar between the arms of the study. The most common grade 3-4 events were neutropenia and elevated creatinine; both observed with similar frequency between treatment groups. In July 2010, we announced the initiation of a worldwide registration trial on a protocol design developed through an 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 first-line metastatic STS entitled PICASSO 3, and is an international, randomized, double-blinded, placebo-controlled trial that enrolled 447 patients. The study completed enrollment in June 2012.

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. The trial was initially designed with PFS as the primary endpoint for accelerated approval, and overall survival, or OS, as the primary endpoint for full approval. In March 2013, we amended the protocol to designate PFS as the primary endpoint for full approval and OS as a secondary endpoint. The trial is powered for both PFS and OS, with PFS

Table of Contents

determined by independent, blinded radiologic review. The Company expects to announce results from this trial, including topline PFS data and an interim OS futility analysis, during the last week of March 2013. The trial is expected to remain blinded for OS. The study is also being submitted as a late-breaking abstract for the annual meeting of the American Society of Clinical Oncology (ASCO). 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 multiple occasions to review all available study data and in all instances has recommended trial continuation. We have obtained Orphan Drug Designation for palifosfamide in both the United States and the European Union for the treatment of STS.

In February 2012, we announced positive preliminary 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, or ITT, hazard ratio of 0.79 and a modified Intent to Treat, or mITT, hazard ratio of 0.78. At 2-years after starting treatment, approximately 40% of subjects treated with palifosfamide are alive and 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).

A Phase 1 trial has been completed with palifosfamide in combination with etoposide and carboplatin. Data informed appropriate dosing for initiating a potentially pivotal, adaptive Phase 3 trial in first-line, metastatic SCLC. In June 2012, the Company initiated an international, multi-center, open-label, adaptive, randomized study of palifosfamide in combination with carboplatin and etoposide, or PaCE, chemotherapy versus carboplatin and etoposide, or CE, alone in chemotherapy naïve patients with metastatic small cell lung cancer, which we refer to as MATISSE. The MATISSE study is designed to enroll up to 548 patients. The trial s primary endpoint is overall survival. Secondary endpoints include progression-free survival, objective response rate and quality of life. MATISSE is being conducted at centers in North America, Europe, Australia, Africa and Asia. In the first quarter of 2013, the IDMC for the MATISSE study conducted an early analysis of safety data after 20 patients had received at least two chemotherapy cycles and recommended the study proceed as planned.

The study s adaptive design includes a prospectively planned opportunity for modification of the study protocol by adjusting one or more specified components of the design in order to maintain adequate power. Evaluation of the study s powering will be conducted by an IDMC at a single, pre-planned interim analysis, scheduled to occur following 125 events. At the interim analysis, the IDMC will review all efficacy and safety data and decide whether to: 1) halt the study for efficacy or futility, 2) continue the study to its planned enrollment of 548 patients, 3) decrease sample size, or 4) increase event size.

Additionally, an oral form of palifosfamide has an active Investigational New Drug, or IND, application to support commencing Phase 1 study.

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 Therapeutic System®, or RTS®, 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.

Table of Contents

Clinical Development Plan for DNA-based therapeutics. The Company completed enrollment in a Phase 1b dose escalation study of ZIN-CTI-001 in the second quarter of 2012 in the United States. ZIN-CTI-001 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 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 one patient having a RECIST PR of >11 months and three patients demonstrating stable disease by RECIST, for an overall disease control rate of 50%. Treatment was generally well-tolerated, 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.

Clinical study of ZIN-ATI-001, essentially ZIN-CTI-001 without dendritic cells, is in an ongoing Phase 1/2 study for metastatic melanoma. The Phase 1b study is evaluating safety in addition to immunological and biological effects and efficacy of the therapeutic candidate in patients with melanoma. Enrollment in the Phase 1 portion of the study is complete and we expect the clinical portion of the study to be complete in the first quarter of 2013.

In the Phase 1 portion of the study, clinical activity was observed in five of seven (71%) patients dosed at the two highest dose levels. The data also showed a correlation between T-cell immune responses and clinical outcome, with no dose-limiting toxicities reported. A total of 13 patients were enrolled in the Phase 1 study, and were treated with a range of doses of an orally administered activator ligand. Three serious adverse events (SAE) were reported: two related to therapy (pyrexia and cytopenia), and one unrelated (deep vein thrombosis). Unrelated to the study therapy, one patient death was reported due to bacterial sepsis and progression of disease. We expect to submit full results of the study for presentation at a major medical meeting.

We recently announced that dosing of the first patient occurred in a Phase 2 study of ZIN-ATI-001. It is a multi-center, single-arm, open-label expansion study that will enroll up to 15 patients with unresectable Stage III or IV melanoma and further evaluate the safety and efficacy of intratumoral injections of ZIN-ATI-001 in combination with an oral activator ligand. Data from this study are expected in the second half of 2013.

Additionally, we plan to initiate a Phase 2 trial of ZIN-ATI-001 and palifosfamide for breast cancer in the second quarter of 2013. It will be a randomized, open-label trial of ZIN-ATI-001 monotheraphy or in combination with palifosfamide in patients with recurrent or metastatic breast cancer and accessible lesions that will enroll up to 68 patients.

Table of Contents

Furthermore, we are evaluating other potential preclinical candidates and continuing discovery efforts aimed at identifying other potential product candidates under our Channel Agreement with Intrexon.

Indibulin, 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 as 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 with the expected convenience of once daily dosing we believe is a significant commercial opportunity.

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 to date 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 difficulty in establishing an 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 with the five days on and nine days off schedule.

Darinaparsin , 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

Table of Contents

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 IV studies of 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 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 first-line setting of PTCL was ended. A Phase 1 trial in solid tumors with an oral form of darinaparsin has completed enrollment. 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. Further, clinical studies are currently ongoing with Solasia.

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 able to successfully develop and commercialize palifosfamide, these competitors have or can market products that could adversely impact the potential commercial success of this product candidate. 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.

Table of Contents

Other treatments for cancer that may 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, (collectively 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 Investigation New Drug application, or 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.

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 i.e. 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, 2010, 2011 or 2012.

Table of Contents

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 referenced. We expensed a $100 thousand milestone payment upon achieving Phase 2 milestones during the year ended December 31, 2006. On March 16, 2010, we expensed a $100 thousand milestone payment upon receiving a United States Patent for palifosfamide. In October 2010, we expensed a $300 thousand milestone payment upon achieving Phase 3 milestones. No milestones under the license agreement have been reached or expensed since 2010. 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. In October 2010, an additional 6,904 shares vested upon the achievement of Phase 3 milestones and were subsequently exercised in 2011. The remaining options will vest upon the 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. 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, or the Option Agreement, 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 isophosphoramide mustard analogs.

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. 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, 2008, 2009, 2010, 2011 and 2012. 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 thousand. 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 since the agreement s inception.

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

Table of Contents

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, 2010 or 2011. During the year ended December 31, 2012, a milestone of $250 thousand was reached and expensed.

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 to the financial statements, Financings)

Following the first 24 months of the agreement, Intrexon may 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.

Table of Contents

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 in a pivotal trial, which trial uses a dosing Regime 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. The agreement was extended through November 8, 2012 and has now expired. We expensed $240 thousand during the years ended December 31, 2010 and 2011, and $200 thousand during the year ended December 31, 2012 for consulting services per the aforementioned agreement. No milestones under the collaboration agreement were reached or expensed during the years ended December 31, 2010, 2011 or 2012.

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.

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.

Table of Contents

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 are party to a Master Clinical Research Organization Services Agreement with PPD Development, L.P., or PPD 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 $23.0 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. During the year ended December 31, 2012, additional enrollment-based and contract modification milestones were met and expensed totaling $3.8 million.

CRO Services Agreement with Pharmaceutical Research Associates, Inc.

On December 13, 2011, we entered into a Master Clinical Research Organization Services Agreement with Pharmaceutical Research Associates, Inc., or PRA, under which PRA provides CRO services in support of our clinical trials. PRA is entitled to cumulative payments of up to $19.7 million under these arrangements, which is payable by us in varying amounts upon PRA achieving specified milestones. During the year ended December 31, 2012, we expensed $7.3 million upon the achievement of various letter of intent and enrollment-based milestones.

CRO Services Agreement with Novella Clinical, Inc.

On December 4, 2008, we entered into a Master Clinical Research Organization Services Agreement with Novella Clinical, Inc., or Novella, under which PRA provides CRO services in support of our clinical trials. The work order for the current trial being conducted by Novella was signed on November 2, 2012. Novella is entitled to cumulative payments of up to $789 thousand under these arrangements, which is payable by us in varying amounts upon Novella achieving specified milestones. During the year ended December 31, 2012, we expensed $256 thousand upon the achievement of various milestones.

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

Table of Contents

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.

Additional information as of February 15, 2013 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 four issued U.S. patents (two of which are scheduled to expire in 2029, one of which is scheduled to expire in 2027 and one of which is scheduled to expire in 2020), four pending U.S. patent applications, twenty issued foreign patents in Europe, Canada, Japan and Australia and four other countries and forty-five pending foreign patent applications in Europe, Canada, Japan, Australia and thirteen 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-seven issued U.S. patents (one of which is scheduled to expire in 2029, three of which are scheduled to expire in 2026, four of which are scheduled to expire in 2025, four of which are scheduled to expire in 2024, two of which are scheduled to expire in 2023, six of which are scheduled to expire in 2022, five of which are scheduled to expire in 2021, one of which is scheduled to expire in 2020 and one of which is scheduled to expire in 2018), forty-nine pending U.S. patent applications, one-hundred-ninety-eight issued foreign patents in Europe, Canada, Japan, Australia and ten other countries, and two-hundred-twenty pending foreign patent applications in Europe, Canada, Japan, Australia and fourteen other countries. The term of one or more of the issued patents may be extended due to the regulatory approval process.

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), six pending U.S. patent applications, one-hundred-forty-six issued foreign patents in Europe, Canada, Japan, Australia and sixteen other countries, and forty-four pending

Table of Contents

foreign patent applications in Europe, Canada, Japan, Australia and eight 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 eight issued U.S. patents (two of which are scheduled to expire in 2029, two of which are scheduled to expire in 2026, one of which is scheduled to expire in 2025 and three of which are scheduled to expire in 2023), eight pending U.S. patent applications, twenty-one issued foreign patents in Europe, Japan, Australia and five other countries and sixty pending foreign patent applications in Europe, Canada, Japan, Australia and eleven 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 biologics under the Public Health Service Act, or PSHA, as well as their respective 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 or Biologics License Applications, or BLAs, warning letters, product recalls, product seizures, total or partial suspension of production or distribution, injunctions, and/or criminal prosecution. Moreover, if our product candidates are approved by the FDA, government coverage and reimbursement policies will both directly and indirectly affect our ability to successfully commercialize our product candidates, and such coverage and reimbursement policies will be affected by future healthcare reform measures. In addition, we may be subject to state and federal laws, including anti-kickback statutes and false claims statutes as well as data privacy laws that restrict certain business practices in the biopharmaceutical industry.

Product Approval Process. None of our product candidates may be marketed in the United States until it has received FDA approval. The steps required before a drug or biologic product 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;
- Adequate and well-controlled human clinical trials to establish the safety and efficacy of the product for each indication;
- Submission to the FDA of NDA or BLA;
- Satisfactory completion of an FDA inspection of the manufacturing facility or facilities at which the product 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, pharmacokinetics, toxicity, immunogenicity and formulation, as well as animal studies. The conduct of the preclinical tests and formulation of the products 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 applies a clinical hold and raises safety

17

Table of Contents

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 or biologic 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 product 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 product 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 product 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 or BLA. 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 the 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 product candidate, are submitted to the FDA in the form of an NDA or BLA 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 external 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.

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

- Is the product safe and effective in its proposed use(s), and do its benefits outweigh its risks?
- Is the product s proposed labeling (package insert) appropriate, and what should it contain? Are measures necessary to mitigate risks of use of the product (referred to as Risk Evaluation and Mitigation Strategies, or REMS)?
- Are the methods used in manufacturing the product and the controls used to maintain its quality adequate to preserve identity, strength, quality, and purity?

The FDA has various programs, including 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

Table of Contents

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.

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. 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 or biologic 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 the 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.

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 or BLA, 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

Table of Contents

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.

Coverage and Reimbursement. Market acceptance and sales of any product candidates that we develop will depend on coverage and reimbursement policies of third-party payors and may be affected by future healthcare reform measures. Government health administration authorities, private health insurers and other organizations generally decide which drugs they will pay for and establish reimbursement levels for health care. In particular, in the U.S., private health insurers and other third-party payers often provide reimbursement for products and services based on the level at which the government (through the Medicare or Medicaid programs) provides reimbursement for such treatments. In the U.S., the European Union and other potentially significant markets for our product candidates, government authorities and third-party payers are increasingly attempting to limit or regulate the price of medical products and services, particularly for new and innovative products and therapies, which has resulted in lower average selling prices. Further, the increased emphasis on managed healthcare in the U.S. and on country and regional pricing and reimbursement controls in the European Union will put additional pressure on product pricing, reimbursement and usage, which may adversely affect our future product sales and results of operations. These pressures can arise from rules and practices of managed care groups, judicial decisions and governmental laws and regulations related to Medicare, Medicaid and healthcare reform, pharmaceutical reimbursement policies and pricing in general.

In the United States and foreign jurisdictions, there have been a number of legislative and regulatory changes to the healthcare system that could affect our future results of operations. In particular, there have been and continue to be a number of initiatives at the United States federal and state level that seek to reduce healthcare costs. The Medicare Prescription Drug, Improvement, and Modernization Act of 2003, or the MMA, imposed new requirements for the distribution and pricing of prescription drugs for Medicare beneficiaries. Under Part D, Medicare beneficiaries may enroll in prescription drug plans offered by private entities which provide coverage of outpatient prescription drugs. Part D plans include both stand-alone prescription drug benefit plans and prescription drug coverage as a supplement to Medicare Advantage plans. Unlike Medicare Part A and B, Part D coverage is not standardized. Part D prescription drug plan sponsors are not required to pay for all covered Part D drugs, and each drug plan can develop its own drug formulary that identifies which drugs it will cover and at what tier or level. However, Part D prescription drug formularies must include drugs within each therapeutic category and class of covered Part D drugs, though not necessarily all the drugs in each category or class. Any formulary used by a Part D prescription drug plan must be developed and reviewed by a pharmacy and

Table of Contents

therapeutic committee. Government payment for some of the costs of prescription drugs may increase demand for our products for which we receive marketing approval. However, any negotiated prices for our future products covered by a Part D prescription drug plan will likely be lower than the prices we might otherwise obtain. Moreover, while the MMA applies only to drug benefits for Medicare beneficiaries, private payors often follow Medicare coverage policy and payment limitations in setting their own payment rates. Any reduction in payment that results from Medicare Part D may result in a similar reduction in payments from non-governmental payors.

The American Recovery and Reinvestment Act of 2009 provides funding for the federal government to compare the effectiveness of different treatments for the same illness. A plan for the research will be developed by the Department of Health and Human Services, the Agency for Healthcare Research and Quality and the National Institutes for Health, and periodic reports on the status of the research and related expenditures will be made to Congress. Although the results of the comparative effectiveness studies are not intended to mandate coverage policies for public or private payors, it is not clear what effect, if any, the research will have on the sales of any product, if any such product or the condition that it is intended to treat is the subject of a study. It is also possible that comparative effectiveness research demonstrating benefits in a competitor s product could adversely affect the sales of our product candidates. If third-party payors do not consider our products to be cost-effective compared to other available therapies, they may not cover our products as a benefit under their plans or, if they do, the level of payment may not be sufficient to allow us to sell our products on a profitable basis.

The U.S. and some foreign jurisdictions are considering or have enacted a number of additional legislative and regulatory proposals to change the healthcare system in ways that could affect our ability to sell our products profitably. Among policy makers and payers in the U.S. and elsewhere, there is significant interest in promoting changes in healthcare systems with the stated goals of containing healthcare costs, improving quality and/or expanding access. In the U.S., the pharmaceutical industry has been a particular focus of these efforts and has been significantly affected by major legislative initiatives, including, most recently, the Patient Protection and Affordable Care Act, as amended by the Health Care and Education Affordability Reconciliation Act, or collectively, the PPACA, which became law in the U.S. in March 2010 and substantially changes the way healthcare is financed by both governmental and private insurers.

Federal and State Fraud and Abuse Laws. In addition to FDA restrictions on marketing of pharmaceutical products, several other types of state and federal laws have been applied to restrict certain business practices in the biopharmaceutical industry in recent years. These laws include anti-kickback and false claims statutes.

The federal Anti-Kickback Statute prohibits, among other things, knowingly and willfully offering, paying, soliciting, or receiving remuneration to induce or in return for purchasing, leasing, ordering, or arranging for the purchase, lease, or order of any healthcare item or service reimbursable under Medicare, Medicaid, or other federally financed healthcare programs. The term remuneration has been broadly interpreted to include anything of value, including for example, gifts, discounts, the furnishing of supplies or equipment, credit arrangements, payments of cash, waivers of payment, ownership interests and providing anything at less than its fair market value. The Anti-Kickback Statute has been interpreted to apply to arrangements between pharmaceutical manufacturers on one hand and prescribers, purchasers, and formulary managers on the other. Although there are a number of statutory exemptions and regulatory safe harbors protecting certain common activities from prosecution, the exemptions and safe harbors are drawn narrowly, and our practices may not in all cases meet all of the criteria for statutory exemptions or safe harbor protection. Practices that involve remuneration that may be alleged to be intended to induce prescribing, purchases, or recommendations may be subject to scrutiny if they do not qualify for an exemption or safe harbor. Several courts have interpreted the statute s intent requirement to mean that if any one purpose of an arrangement involving remuneration is to induce referrals of federal healthcare covered business, the statute has been violated. The reach of the Anti-Kickback Statute was also broadened by the PPACA, which, among other things, amends the intent requirement of the federal Anti-Kickback Statute. Pursuant to the statutory amendment, a person or entity no longer needs to have actual knowledge of this statute or specific intent to violate it in order to have committed a violation.

Table of Contents

In addition, the PPACA provides that the government may assert that a claim including items or services resulting from a violation of the federal Anti-Kickback Statute constitutes a false or fraudulent claim for purposes of the civil False Claims Act (discussed below) or the civil monetary penalties statute, which imposes penalties against any person who is determined to have presented or caused to be presented a claim to a federal health program that the person knows or should know is for an item or service that was not provided as claimed or is false or fraudulent.

The federal False Claims Act prohibits any person from knowingly presenting, or causing to be presented, a false claim for payment to the federal government or knowingly making, using, or causing to be made or used a false record or statement material to a false or fraudulent claim to the federal government. As a result of a modification made by the Fraud Enforcement and Recovery Act of 2009, a claim includes any request or demand for money or property presented to the U.S. government. Recently, several pharmaceutical and other healthcare companies have been prosecuted under these laws for allegedly providing free product to customers with the expectation that the customers would bill federal programs for the product. Other companies have been prosecuted for causing false claims to be submitted because of the companies marketing of the product for unapproved, and thus non-reimbursable, uses. Many states also have statutes or regulations similar to the federal Anti-Kickback Statute and False Claims Act, which state laws apply to items and services reimbursed under Medicaid and other state programs, or, in several states, apply regardless of the payer. Also, the federal Health Insurance Portability and Accountability Act of 1996, or HIPAA, created new federal criminal statutes that prohibit knowingly and willfully executing a scheme to defraud any healthcare benefit program, including private third-party payers and knowingly and willfully falsifying, concealing or covering up a material fact or making any materially false, fictitious or fraudulent statement in connection with the delivery of or payment for healthcare benefits, items or services.

Because of the breadth of these laws and the narrowness of the federal Anti-Kickback Statute s safe harbors, it is possible that some of our business activities could be subject to challenge under one or more of such laws. Such a challenge could have a material adverse effect on our business, financial condition and results of operations. If we obtain FDA approval for any of our product candidates and begin commercializing those products in the United States, our operations may be directly, or indirectly, through our customers, distributors, or other business partners, subject to various federal and state fraud and abuse laws, including, without limitation, anti-kickback statutes and false claims statutes. These laws may impact, among other things, our proposed sales, marketing and education programs.

In addition, we may be subject to data privacy and security regulation by both the federal government and the states in which we conduct our business. HIPAA, as amended by the Health Information Technology and Clinical Health Act, or HITECH, and its implementing regulations, imposes certain requirements relating to the privacy, security and transmission of individually identifiable health information. Among other things, HITECH makes HIPAA s privacy and security standards directly applicable to business associates independent contractors or agents of covered entities that receive or obtain protected health information in connection with providing a service on behalf of a covered entity. HITECH also increased the civil and criminal penalties that may be imposed against covered entities, business associates and possibly other persons, and gave state attorneys general new authority to file civil actions for damages or injunctions in federal courts to enforce the federal HIPAA laws and seek attorney s fees and costs associated with pursuing federal civil actions. In addition, state laws govern the privacy and security of health information in certain circumstances, many of which differ from each other in significant ways and may not have the same effect, thus complicating compliance efforts.

If our operations are found to be in violation of any of the federal and state laws described above or any other governmental regulations that apply to us, we may be subject to penalties, including criminal and significant civil monetary penalties, damages, fines, imprisonment, exclusion of products from reimbursement under government programs, and the curtailment or restructuring of our operations, any of which could adversely affect our ability to operate our business and our results of operations. To the extent that any of our product candidates are ultimately sold in a foreign country, we may be subject to similar foreign laws and regulations, which may

Table of Contents

include, for instance, applicable post-marketing requirements, including safety surveillance, anti-fraud and abuse laws, and implementation of corporate compliance programs and reporting of payments or transfers of value to healthcare professionals.

Employees

As of February 15, 2013, we had 83 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 ongoing 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, 2012, we had a net loss of $96.1 million, and, as of December 31, 2012, we have incurred approximately $283.7 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 anticipate that our cash resources will be sufficient to fund our operations into the second half of 2013 and we have no current committed sources of additional capital. As a result, our independent registered public accounting firm has expressed a substantial doubt about our ability to continue as a going concern in their report on our financial statements. 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, 2012, we had incurred approximately $283.7 million of cumulative net losses and had approximately $73.3 million of cash and cash equivalents. We anticipate that our cash resources will be sufficient

Table of Contents

to fund our operations into the second half of 2013. The results from the Company s PICASSO 3 pivotal trial in first-line STS are expected in the last week of March 2013. The Company has various dilutive and non-dilutive funding alternatives if the results are positive. If the results are negative, alternative cost-cutting efficiencies are planned in an attempt to extend our cash resources as long as possible, though there are no assurances that such efforts, if necessary, would be realized. In addition, changes may occur that would consume our existing capital prior to the second half of 2013, including expansion of the scope of, and/or slower than expected progress of, our research and development efforts and changes in governmental regulation. As a result, our independent registered public accounting firm has expressed a substantial doubt about our ability to continue as a going concern in their report on our financial statements. 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 have estimated the sufficiency of our cash resources based in part on the trial design for our PICASSO 3 pivotal trial in first-line STS and our adaptive Phase 3 trial in first-line SCLC for IV palifosfamide and our current timing expectations for the results of the PICASSO 3 pivotal trial and enrollment in our adaptive Phase 3 trial in first-line SCLC for IV palifosfamide, which may change based on the progression of enrollment. 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.

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:

Unforeseen safety issues;

Determination of dosing issues;

Table of Contents

Lack of effectiveness during clinical trials;

Slower than expected rates of patient recruitment and enrollment;

Inability to monitor patients adequately during or after treatment;

Inability or unwillingness of medical investigators to follow our clinical protocols; and

Regulatory determinations to temporarily or permanently cease enrollment for other reasons not related to patient safety.

We commenced the PICASSO 3 pivotal trial for IV palifosfamide early in the third quarter of 2010 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. 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 completed full enrollment in June 2012. The outcome in progression-free survival, the study s primary endpoint for full approval, is expected in the last week of March 2013. 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 primary endpoint, or the primary endpoint is delayed for other reasons, the delay will postpone our receipt of results from the trial and, consequently, our ability, if positive, 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 designations for palifosfamide for the treatment of soft tissue sarcomas and darinaparsin for the treatment of peripheral T-cell lymphoma in both the United States and Europe, and we may be able to receive additional Orphan Drug designation from the FDA and EMA for other product candidates. In the United States, orphan designation is available to drugs intended to treat, diagnose or prevent a rare disease or condition that affects fewer than 200,000 people in the U.S. at the time of application for orphan designation. Orphan designation qualifies the sponsor of the product for the tax credit and marketing incentives. The first sponsor to receive FDA marketing approval for a drug with an orphan designation is entitled to a seven-year exclusive marketing period in the U.S. for that product for that indication and, typically, a waiver of the prescription drug user fee for its marketing application. However, a drug that the FDA considers to be clinically superior to, or different from, another approved orphan drug, even though for the same indication, may also obtain approval in the U.S. during the seven-year exclusive marketing period. Orphan drug exclusive marketing rights may also be lost if the FDA later determines that the request for designation was materially defective or if the manufacturer is unable to assure sufficient quantity of the drug. There is no guarantee that any of our other product candidates will receive Orphan Drug designation 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

Table of Contents

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.

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

Our Channel Agreement 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 having completed a Phase 1b study and ZIN-ATI-001 currently in a Phase 2 study, both in melanoma. 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 Channel Agreement with Intrexon.

We will incur additional expenses in connection with our Channel Agreement with Intrexon Corporation.

The *in vivo* effector platform, in which we have acquired rights for cancer from Intrexon, includes two existing product candidates, DC-RTS-IL-12 and Ad-RTS-IL-12. Upon entry into the Channel Agreement 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 Channel Agreement 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;
- Participating in regulatory approval process;
- Formulating and manufacturing products; and
- Conducting sales and marketing activities.

Table of Contents

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

Because we currently neither have nor intend to establish internal research capabilities, we are dependent upon pharmaceutical and biotechnology companies and academic and other researchers to sell or license us their product candidates 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, 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, Dr. Hagop Youssoufian, our President of Research & Development and Chief Medical Officer, Jason A. Amello, our Executive Vice President and Chief Financial Officer, Caesar J. Belbel, our Executive Vice President and Chief Legal Officer and our principal scientific, regulatory, and medical advisors. Dr. Lewis , Dr. Youssoufian s, Mr. Amello s and Mr. Belbel s employment are governed by written employment agreements. The employment agreement with Dr. Lewis provides for a term that expires in January 2014. Drs. Lewis and Youssoufian, and Messrs. Amello 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. Amello 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.

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 submit an NDA or BLA to the FDA and any failure or delay in completing clinical trials for our product candidates could harm our business.

Our product candidates are in various stages of development and require extensive clinical testing. Notwithstanding our current clinical trial plans for each of our existing product candidates, we may not be able to commence additional trials or see results from these trials within our anticipated timelines. As such, we cannot predict with any certainty if or when we might submit an NDA 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.

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

30

Table of Contents

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.

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

Table of Contents

manufacturing practices, or cGMP, 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.

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

Table of Contents

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 healthcare 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 coverage and adequate 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 do not receive coverage from payors, 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 coverage and reimbursement will be available from:

Government and health administration authorities;

Private health maintenance organizations and health insurers; and

Other healthcare payers.

Patients who are prescribed medicine for the treatment of their conditions generally rely on third-party payors to reimburse all or part of the costs associated with their prescription drugs. Adequate coverage and reimbursement from governmental healthcare programs, such as Medicare and Medicaid, and commercial payors is critical to new product acceptance. Coverage decisions may depend upon clinical and economic standards that disfavor new drug products when more established or lower cost therapeutic alternatives are already available or subsequently become available. Even if we obtain coverage for our product candidates, the resulting reimbursement payment rates might not be adequate or may require co-payments that patients find unacceptably high. Patients are unlikely to use our product candidates unless coverage is provided and reimbursement is adequate to cover a significant portion of the cost of our product candidates.

Table of Contents

In addition, the market for our product candidates for which we may receive regulatory approval will depend significantly on access to third-party payors drug formularies, or lists of medications for which third-party payors provide coverage and reimbursement. The industry competition to be included in such formularies often leads to downward pricing pressures on pharmaceutical companies. Also, third-party payors may refuse to include a particular branded drug in their formularies or otherwise restrict patient access to a branded drug when a less costly generic equivalent or other alternative is available.

Third-party payors, whether foreign or domestic, or governmental or commercial, are developing increasingly sophisticated methods of controlling healthcare costs. In addition, in the United States, no uniform policy of coverage and reimbursement for drug products exists among third-party payors. Therefore, coverage and reimbursement for drug products can differ significantly from payor to payor. As a result, the coverage determination process is often a time-consuming and costly process that requires us to provide scientific and clinical support for the use of our products to each payor separately, with no assurance that approval will be obtained. If we are unable to obtain coverage of and adequate 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, results of operations, financial condition, and future success.

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. For example, the Medicare Prescription Drug, Improvement, and Modernization Act of 2003 established a new Part D prescription drug benefit, which became effective January 1, 2006. Under the prescription drug benefit, Medicare beneficiaries can obtain prescription drug coverage from private sector plans that are permitted to limit the number of prescription drugs that are covered in each therapeutic category and class on their formularies. If any of our product candidates that are approved by the FDA are not widely included on the formularies of these plans, our ability to market our products to the Medicare population could suffer.

Furthermore, there have been and continue to be a number of initiatives at the federal and state level that seek to reduce healthcare costs. Most recently, in March 2010, President Obama signed into law the Patient Protection and Affordable Health Care Act, as amended by the Health Care and Education Affordability Reconciliation Act, or collectively the PPACA, which includes measures to significantly change the way healthcare is financed by both governmental and private insurers. Among the provisions of the PPACA of importance to the pharmaceutical industry are the following:

- an annual, nondeductible fee on any entity that manufactures or imports certain branded prescription drugs and biologic agents, apportioned among these entities according to their market share in certain government healthcare programs, beginning in 2011;

- an increase in the statutory minimum rebates a manufacturer must pay under the Medicaid Drug Rebate Program, retroactive to January 1, 2010, to 23% and 13% of the average manufacturer price for most branded and generic drugs, respectively;

- a new Medicare Part D coverage gap discount program, in which manufacturers must agree to offer 50% point-of-sale discounts off negotiated prices of applicable brand drugs to eligible beneficiaries during their coverage gap period, as a condition for the manufacturer s outpatient drugs to be covered under Medicare Part D, beginning in 2011;

- extension of manufacturers Medicaid rebate liability to covered drugs dispensed to individuals who are enrolled in Medicaid managed care organizations, effective March 23, 2010;

- expansion of eligibility criteria for Medicaid programs by, among other things, allowing states to offer Medicaid coverage to additional individuals beginning in April 2010 and by adding new mandatory eligibility categories for certain individuals with income at or below 133% of the Federal Poverty Level beginning in 2014, thereby potentially increasing both the volume of sales and manufacturers Medicaid rebate liability;

Table of Contents

expansion of the entities eligible for discounts under the Public Health Service pharmaceutical pricing program, effective in January 2010;

new requirements to report certain financial arrangements with physicians and teaching hospitals, as defined in the PPACA and its implementing regulations, including reporting any transfer of value made or distributed to teaching hospitals, prescribers, and other healthcare providers and reporting any ownership and investment interests held by physicians and their immediate family members and applicable group purchasing organizations during the preceding calendar year, with data collection to be required beginning August 1, 2013 and reporting to the Centers for Medicare & Medicaid Services, or CMS, to be required by March 31, 2014 and by the 90th day of each subsequent calendar year;

a new requirement to annually report drug samples that manufacturers and distributors provide to physicians, effective April 1, 2012;

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

a licensure framework for follow-on biologic products;

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

creation of the Independent Payment Advisory Board which, beginning in 2014, will have authority to recommend certain changes to the Medicare program that could result in reduced payments for prescription drugs and those recommendations could have the effect of law even if Congress does not act on the recommendations; and

establishment of a Center for Medicare Innovation at CMS to test innovative payment and service delivery models to lower Medicare and Medicaid spending, potentially including prescription drug spending beginning by January 1, 2011.

Many of the details regarding the implementation of the PPACA are yet to be determined, and at this time, it remains unclear the full effect that the PPACA would have on our business. On June 28, 2012, the U.S. Supreme Court upheld the constitutionality of the PPACA, excepting certain provisions that would have required each state to expand its Medicaid programs or risk losing all of the state s Medicaid funding. At this time, it remains unclear whether there will be any further changes made to the PPACA, whether in part or in its entirety. Some states have indicated that they intend to not implement certain sections of the PPACA, and some members of the US Congress are still working to repeal the PPACA. We cannot predict whether these challenges will continue or other proposals will be made or adopted, or what impact these efforts may have on us.

In addition, in many foreign countries, particularly the countries of the European Union, the pricing of prescription drugs is subject to government control. In some non-U.S. jurisdictions, the proposed pricing for a drug must be approved before it may be lawfully marketed. The requirements governing drug pricing vary widely from country to country. For example, the EU provides options for its member states to restrict the range of medicinal products for which their national health insurance systems provide reimbursement and to control the prices of medicinal products for human use. A member state may approve a specific price for the medicinal product or it may instead adopt a system of direct or indirect controls on the profitability of the company placing the medicinal product on the market. 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.

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.

35

Table of Contents

If we fail to comply with federal and state healthcare laws, including fraud and abuse and health information privacy and security laws, we could face substantial penalties and our business, results of operations, financial condition and prospects could be adversely affected.

As a pharmaceutical company, even though we do not and will not control referrals of healthcare services or bill directly to Medicare, Medicaid or other third-party payors, certain federal and state healthcare laws and regulations pertaining to fraud and abuse and patients rights are and will be applicable to our business. We could be subject to healthcare fraud and abuse and patient privacy regulation by both the federal government and the states in which we conduct our business. The laws that may affect our ability to operate include:

- the federal Anti-Kickback Statute, which constrains our marketing practices, educational programs, pricing policies, and relationships with healthcare providers or other entities, by prohibiting, among other things, soliciting, receiving, offering or paying remuneration, directly or indirectly, to induce, or in return for, either the referral of an individual or the purchase or recommendation of an item or service reimbursable under a federal healthcare program, such as the Medicare and Medicaid programs;

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

- the federal Health Insurance Portability and Accountability Act of 1996, or HIPAA, which created new federal criminal statutes that prohibit executing a scheme to defraud any healthcare benefit program or making false statements relating to healthcare matters;

- HIPAA, as amended by the Health Information Technology for Economic and Clinical Health Act of 2009, or HITECH, and its implementing regulations, which imposes certain requirements relating to the privacy, security and transmission of individually identifiable health information; and

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

Because of the breadth of these laws and the narrowness of the statutory exceptions and safe harbors available under the U.S. federal Anti-Kickback Statute, it is possible that some of our business activities could be subject to challenge under one or more of such laws. To the extent that any of our product candidates is ultimately sold in a foreign country, we may be subject to similar foreign laws and regulations. If we or our operations are found to be in violation of any of the laws described above or any other governmental regulations that apply to us, we may be subject to penalties, including civil and criminal penalties, damages, fines, exclusion from participation in U.S. federal or state health care programs, and the curtailment or restructuring of our operations. Any penalties, damages, fines, curtailment or restructuring of our operations could materially adversely affect our ability to operate our business and our financial results. Although compliance programs can mitigate the risk of investigation and prosecution for violations of these laws, the risks cannot be entirely eliminated. Any action against us for violation of these laws, even if we successfully defend against it, could cause us to incur significant legal expenses and divert our management s attention from the operation of our business. Moreover, achieving and sustaining compliance with applicable federal and state privacy, security and fraud laws may prove costly.

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%

36

Table of Contents

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;
- Whether or not others will obtain patents claiming subject matter related to or relevant to our product candidates; 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 America 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. As the U.S. Patent and Trademark Office continues to implement the Leahy-Smith Act, and as the federal courts have the opportunity to interpret the Leahy-Smith Act, the laws and regulations governing patents, and the rules regarding patent procurement 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.

Table of Contents

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 or derivation of inventions, or post-grant review, inter partes review, or reexamination proceedings reviewing the patentability of our patented claims. In addition, any foreign patents that are granted may become subject to opposition, nullity, or revocation proceedings in foreign jurisdictions having such proceedings. The defense and prosecution, if necessary, of intellectual property actions are costly and divert technical and management personnel away from their normal responsibilities.

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 synthetic biology, which we are pursuing under our Channel Agreement 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 synthetic biology, 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

Table of Contents

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 synthetic biology 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 Channel 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 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.

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

Table of Contents

effectiveness of disclosure controls and procedures and of our internal control over financing reporting in order to allow management to report on such controls. Sarbanes-Oxley generally requires that a public reporting company s independent registered public accounting firm attest to the effectiveness of the company s internal control over financial reporting as of the end of each fiscal year in the company s annual report on Form 10-K. 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 effect 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 prior to January 6, 2014 without 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.

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.

Table of Contents

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 October 2018. Under the terms of the lease, we lease approximately seven thousand square feet and are required to make rental payments at an average monthly rate of approximately $35 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-six thousand square feet. The Boston office space consists of four 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 $61 thousand through the remainder of the lease term. We also lease office space in Germantown, MD. The Maryland office space is subject to a lease agreement that expires in March 2014. On July 16, 2012, the Germantown, Maryland office was closed. 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, 2012, 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.

	2012		2011	
Quarter Ended	**High**	**Low**	**High**	**Low**
March 31	$ 5.69	$ 4.15	$ 6.25	$ 4.72
June 30	$ 6.00	$ 4.39	$ 7.70	$ 5.88
September 30	$ 6.22	$ 4.97	$ 6.07	$ 4.41
December 31	$ 5.36	$ 3.99	$ 5.20	$ 3.85

Record Holders

As of February 13, 2013, we had approximately 173 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 13, 2013, we had approximately 10,049 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

On November 7, 2012, we issued 3,636,926 shares of our common stock, which we refer to as the Milestone Shares, to Intrexon under the terms of our Stock Purchase Agreement with Intrexon dated January 6, 2011. Under the terms of the Stock Purchase Agreement, we agreed to issue the Milestone Shares under certain conditions upon dosing of the first patient in a ZIOPHARM-conducted Phase 2 clinical trial in the Unites States, or similar study as the parties may agree in a country other than the United States, of a product candidate that is created, produced, developed or identified directly or indirectly by us during the term of the Channel Agreement and that, subject to certain exceptions, involves DNA administered to humans for expression of anti-cancer effectors for the purpose of treatment or prophylaxis of cancer. On October 24, 2012, the Company initiated dosing in a Phase 2 study of ZIN-ATI-001 for unresectable Stage III or IV melanoma, triggering the issuance of the Milestone Shares.

The offer and sale of the Milestone Shares was not registered under the Securities Act of 1933, as amended and, therefore, may not be offered or sold in the United States absent registration or an applicable exemption from registration requirements. For this issuance, we relied on the exemption from federal registration under Section 4(2) of the Securities Act and/or Rule 506 promulgated thereunder, based on our belief that the offer and sale of the shares did not involve a public offering as Intrexon is an accredited investor as defined under Section 501 promulgated under the Securities Act and no general solicitation was involved in the issuance and sale.

Table of Contents

Issuer Purchases of Equity Securities

During the three months ended December 31, 2012, we purchased 107,413 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, 2012:

Period	Total Number of Shares Purchased	Average Price Paid Per Share ($)
October 1 to 31, 2012		$
November 1 to 30, 2012		$
December 1 to 31, 2012	107,413	$ 4.19
Total	107,413	

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, 2007 and tracks it through December 31, 2012.

Table of Contents

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,				
	2012	2011	2010	2009	2008
	(in thousands, except per share amounts)				
Statements of Operations Data:					
Research contract revenue	$ 800	$ 667	$	$	$
Total operating expenses	102,969	72,067	24,546	12,123	25,619
Loss from operations	(102,169)	(71,400)	(24,546)	(12,123)	(25,619)
Other income, net	(13)	39	765	13	388
Change in fair value of warrants	6,050	7,583	(8,889)	4,461	
Net loss	(96,132)	(63,778)	(32,670)	(7,649)	(25,231)
Basic and diluted net loss per share	$ (1.22)	$ (0.97)	$ (0.71)	$ (0.33)	$ (1.19)
Weighted average number of common shares outstanding: basic and diluted	78,546	66,004	46,004	23,108	21,233

	Year Ended December 31,				
	2012	2011	2010	2009	2008
	(in thousands)				
Balance Sheet Data:					
Cash and cash equivalents	$ 73,306	$ 104,713	$ 60,392	$ 48,839	$ 11,379
Total assets	83,404	108,108	61,520	49,736	12,573
Warrant liabilities	12,962	19,425	27,311	18,471	
Total liabilities	34,959	36,501	30,967	21,632	5,834
Stockholders equity	48,445	71,607	30,553	28,104	6,739

Table of Contents

Item 7. Management Discussion and Analysis of Financial Condition and Results of Operations

The following Management s Discussion and Analysis of Financial Condition and Results of Operations, as well as disclosures included under the heading Business and elsewhere in this Form 10-K, include forward-looking statements within the meaning of the Private Securities Litigation Reform Act of 1995. This Act provides a safe harbor for forward-looking statements to encourage companies to provide prospective information about themselves so long as they identify these statements as forward-looking and provide meaningful cautionary statements identifying important factors that could cause actual results to differ from the projected results. All statements other than statements of historical fact we make in this Form 10-K are forward-looking. In particular, statements preceded by, followed by or that include the words intends , estimates , plans , believes , expects , anticipates , should , could or similar expressions, are forward-looking statements. These statements but are not limited to, statements regarding future sales and operating results; growth and trends of our company and our industry, generally; growth of the markets in which we participate; international events; product performance; the acquisition of or investment in other entities; the construction of new or refurbishment of existing facilities by us; our ability to successfully develop and commercialize our therapeutic products; our ability to expand our long-term business opportunities; financial projections and estimates and their underlying assumptions; and future performance. All of such statements are subject to certain risks and uncertainties, many of which are difficult to predict and generally beyond our control, that could cause actual results to differ materially from those expressed in, or implied or projected by, the forward-looking information and statements. These risks and uncertainties include, but are not limited to: whether Palifosfamide, Ad-RTS IL-12, DC-RTS IL-12, Darinaparsin, Indibulin, or any of our other therapeutic products will advance further in the clinical trials process and whether and when, if at all, they will receive final approval from the FDA or equivalent foreign regulatory agencies and for which indications; whether Palifosfamide, Ad-RTS IL-12, DC-RTS IL-12, Darinaparsin, Indibulin, and our other therapeutic products will be successfully marketed if approved; whether any of our synthetic biology platform discovery and development efforts will be successful; our ability to achieve the results contemplated by our collaboration agreements; the strength and enforceability of our intellectual property rights; competition from pharmaceutical and biotechnology companies; the development of and our ability to take advantage of the market for DNA-based biotherapeutics; our ability to raise additional capital to fund our operations on terms acceptable to us; general economic conditions; and the other risk factors contained in this Annual Report on Form 10-K. Forward-looking statements reflect our current expectations and are inherently uncertain. Our actual results may differ significantly from our expectations. We assume no obligation to update this forward-looking information. The section herein entitled Risk Factors describes some, but not all, of the factors that could cause these differences.

The following discussion and analysis should be read in conjunction with our historical financial statements and the notes to those financial statements which are included in Item 8 of Part II of this Form 10-K.

Business Overview

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 through the licensing and development of proprietary small molecule drug candidates and the synthetic biology platform. Our small molecule drug candidates 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 small molecule clinical programs include palifosfamide (ZIO-201), indibulin (ZIO-301) and darinaparsin (ZIO-101). We are also pursuing the development of our synthetic biology platform 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 stimulate key pathways used by the body s immune system to inhibit the growth and metastasis of cancers, adding significantly to our small molecule drug development portfolio and utilizing

Table of Contents

our capabilities to translate science to the patient setting. More detailed descriptions of palifosfamide, indibulin, darinaparsin, 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.

Development Plans

We are currently pursuing several clinical programs for our small molecule and synthetic biology candidates, which include:

- palifosfamide (ZIO-201) completing our Phase 3 pivotal trial in first-line metastatic STS, entitled PICASSO 3, and continuing enrollment in our Phase 3 trial in SCLC, entitled MATISSE.
- ZIN-CTI-001 completing a Phase 1b trial in patients with metastatic melanoma.
- ZIN-ATI-001 completing a Phase 1b trial in patients with late-stage melanoma, continuing enrollment in our Phase 2 trial in patients with late-stage melanoma and enrolling a Phase 2 trial of ZIN-ATI-001 and palifosfamide for breast cancer.
- indibulin (ZIO-301) completing a Phase 1 trial in patients with metastatic breast cancer.
- darinaparsin (ZIO-101) working with Solasia in the licensed territory; assessing future oral/IV opportunities.

We are also evaluating additional potential preclinical candidates and continuing discovery efforts aimed at identifying other potential product candidates under our Channel Agreement with Intrexon.

Our current plans involve using our principal internal financial resources to develop palifosfamide and to extend the synthetic biology program, with the intention of ultimately partnering or otherwise raising additional resources to support further development activities for all of our product candidates. Based on these plans, we expect to incur the following expenses during the next twelve months: approximately $123.2 million on research and development expenses and approximately $29.1 million on general corporate and administrative expenses. As of December 31, 2012, we had approximately $73.3 million of cash and cash equivalents. This forecast of expenses is forward-looking information that involves risks and uncertainties, and the actual amount of our expenses over the next twelve months could vary materially and adversely as a result of a number of factors, including the factors discussed in the Risk Factors section of this report and the uncertainties applicable to our forecast for the overall sufficiency of our capital resources, which are discussed under Liquidity and Capital Resources below. We have based our estimates on assumptions that may prove to be wrong, and our expenses could prove to be significantly higher than we currently anticipate.

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

Financial Overview

Overview of Results of Operations

Revenue.

We recognize research and development funding revenue over the estimated period of performance. We have not generated product revenues since our inception. Unless and until we receive approval from the FDA and/or other regulatory authorities for our product candidates, we cannot sell our products and will not have product revenues.

46

Table of Contents

Research and Development Expenses.

Our research and development expense consists primarily of salaries and related expenses for personnel, costs of contract manufacturing services, costs of facilities and equipment, fees paid to professional service providers in conjunction with our clinical trials, fees paid to research organizations in conjunction with pre-clinical animal studies, costs of materials used in research and development, consulting, license and milestone payments and sponsored research fees paid to third parties.

We have not accumulated and tracked our internal historical research and development costs or our personnel and personnel-related costs on a program-by-program basis. Our employee and infrastructure resources are allocated across several projects, and many of our costs are directed to broadly applicable research endeavors. As a result, we cannot state the costs incurred for each of our oncology programs on a program-by-program basis.

In 2012, our clinical projects consisted primarily of two Phase 3 projects for our lead product candidate, palifosfamide. The expenses for our Phase 3 palifosfamide study in STS incurred by us to third parties were $14.4 million for the year ended December 31, 2012, and $34.7 million from the project inception in July 2010 through December 31, 2012. The expenses for our Phase 3 palifosfamide study in SCLC incurred by us to third parties were $10.8 million for the year ended December 31, 2012, and $10.8 million from the project inception in December 2011 through December 31, 2012.

Our future research and development expenses in support of our current and future programs will be subject to numerous uncertainties in timing and cost to completion. We test potential products in numerous pre-clinical studies for safety, toxicology and efficacy. We may conduct multiple clinical trials for each product. As we obtain results from trials, we may elect to discontinue or delay clinical trials for certain products in order to focus our resources on more promising products or indications. Completion of clinical trials may take several years or more, and the length of time generally varies substantially according to the type, complexity, novelty and intended use of a product. It is not unusual for pre-clinical and clinical development of each of these types of products to require the expenditure of substantial resources.

We estimate that clinical trials of the type generally needed to secure new drug approval are typically completed over the following timelines:

Clinical Phase	Estimated Completion Period
Phase I	1 - 2years
Phase II	2 - 3years
Phase III	2 - 4years

The duration and the cost of clinical trials may vary significantly over the life of a project as a result of differences arising during clinical development, including, among others, the following:

- the number of clinical sites included in the trials;
- the length of time required to enroll suitable patents;
- the number of patients that ultimately participate in the trials;
- the duration of patient follow-up to ensure the absence of long-term product-related adverse events; and
- the efficacy and safety profile of the product.

As a result of the uncertainties discussed above, we are unable to determine the duration and completion costs of our programs or when and to what extent we will receive cash inflows from the commercialization and sale of a product. Our inability to complete our programs in a timely manner or our failure to enter into appropriate

Table of Contents

collaborative agreements could significantly increase our capital requirements and could inversely impact our liquidity. These uncertainties could force us to seek additional, external sources of financing from time-to-time in order to continue with our product development strategy. Our ability to raise additional capital, or to do so on terms reasonably acceptable to us, would jeopardize the future success of our business.

General and Administrative Expenses.

General and administrative expenses consist primarily of salaries, benefits and stock-based compensation, consulting and professional fees, including patent related costs, general corporate costs and facility costs not otherwise included in research and development expenses or cost of product revenue.

Other Income (Expense).

Other income (expense) consists primarily of changes in the fair value of warrants.

Results of Operations for the fiscal year ended December 31, 2012 versus December 31, 2011

Revenues. Revenues for the years ended December 31, 2012 and 2011 were as follows:

	Year ended December 31,			
	2012	2011	Change	
($ in thousands)				
Collaboration revenue	$ 800	$ 667	$ 133	20%

Revenue for the year ended December 31, 2012 increased by $0.1 million from the year ended December 31, 2011. The increase was due to our receipt of funds under our collaboration agreement with Solasia to further the research and development of darinaparsin. We recognize the research and development funding revenue relating to this collaboration agreement in equal monthly amounts over the estimated period of performance of 75 months commencing March 2011.

Research and Development Expenses. Research and development expenses during the years ended December 31, 2012 and 2011 were as follows:

	Year ended December 31,			
	2012	2011	Change	
($ in thousands)				
Research and development	$ 83,446	$ 57,083	$ 26,363	46%

Research and development expenses for the year ended December 31, 2012 increased by $26.4 million from the year ended December 31, 2011. The increase was due to the following changes since 2011: higher trial costs of $10.8 million related to the Phase 3 palifosfamide study in SCLC, which started in 2012; increased preclinical trial costs of $1.8 million due to additional studies needed to assist in NDA filing preparation; other clinical costs of $0.8 million; manufacturing activity costs of $5.6 million needed to support existing trials and further development of drugs; a $1.3 million increase in non-cash expense related to our Channel Agreement over 2011; salary and employee-related costs of $5.6 million due to increased headcount to support increases in Research and Development activities discussed above; and $0.9 million related to a new safety database, offset by other cost reductions of ($0.4) million.

We expect our research and development expenses to increase, as compared to prior periods, as we continue our pivotal Phase 3 study of palifosfamide and other studies for palifosfamide, DNA therapeutics, indibulin and darinaparsin.

Table of Contents

General and Administrative Expenses. General and administrative expenses during the years ended December 31, 2012 and 2011 were as follows:

($ in thousands)	Year ended December 31, 2012	2011	Change	
General and administrative	$ 19,523	$ 14,984	$ 4,539	30%

General and administrative expenses for the year ended December 31, 2012 increased by $4.5 million from the year ended December 31, 2011. The increase was primarily due to higher salary and higher employee-related costs of $2.0 million to support increased activity in clinical studies, non-employee contracted costs of $1.2 million, costs of $1.0 million related to our restructuring and other costs of $0.3 million.

We expect our general and administrative expenses to increase moderately to support increased activity in clinical studies.

Other Income (Expense). Other income (expense) during the years ended December 31, 2012 and 2011 were as follows:

($ in thousands)	Year ended December 31, 2012	2011	Change	
Other income, net	$ (13)	$ 39	$ (52)	-133%
Change in fair value of warrants	6,050	7,583	$ (1,533)	-20%
Total	$ 6,037	$ 7,622	$ (1,585)	

The decrease in other income (expense) from the year ended December 31, 2012 compared to the year ended December 31, 2011 was due primarily to the change in the fair value of liability-classified warrants, which yielded a gain of $6,050 thousand in 2012 as compared to a gain of $7,583 thousand in 2011. The change in liability-classified warrants is attributable to the decrease in our stock price, decrease in remaining term and a decrease in volatility. Additional changes are attributable to increased state tax refunds and decreased interest rates on invested funds.

Results of Operations for the fiscal year ended December 31, 2011 versus December 31, 2010

Revenues. Revenues for the years ended December 31, 2011 and 2010 were as follows:

($ in thousands)	Year ended December 31, 2011	2010	Change	
Collaboration revenue	$ 667	$	$ 667	100%

Revenue for the year ended December 31, 2011 increased by $0.7 million from the year ended December 31, 2010. The increase was due to our receipt of funds under our collaboration agreement with Solasia to further the research and development of darinaparsin. We recognize the research and development funding revenue relating to this collaboration agreement in equal monthly amounts over the estimated period of performance of 75 months commencing March 2011.

Table of Contents

Research and Development Expenses. Research and development expenses during the years ended December 31, 2011 and 2010 were as follows:

	Year ended December 31,			
	2011	2010	Change	
($ in thousands)				
Research and development	$ 57,083	$ 12,910	$ 44,173	342%

Research and development expenses for the year ended December 31, 2011 increased by $44.2 million from the year ended December 31, 2010. The increase was primarily due to a one-time $17.5 million non-cash expense related to our channel partnership arrangement with Intrexon, including our associated license of Intrexon technology, along with increased clinical costs of $14.4 million, of which $10.5 million related to the Phase 3 palifosfamide study, $3.4 million related to DNA based therapeutics projects and $0.5 million related to other clinical trials, increased preclinical costs of $2.8 million, increased manufacturing activity of $3.9 million to replenish drug supplies and further develop palifosfamide, increased salary and employee-related costs of $5.3 million resulting from additional headcount and other costs of $0.3 million.

Exclusive of the one-time $17.5 million non-cash expense related to our channel partnership arrangement with Intrexon, we expect our research and development expenses to increase, as compared to prior periods, as we continue our pivotal Phase 3 study of palifosfamide and other studies for palifosfamide, DNA therapeutics, indibulin and darinaparsin.

General and Administrative Expenses. General and administrative expenses during the years ended December 31, 2011 and 2010 were as follows:

	Year ended December 31,			
	2011	2010	Change	
($ in thousands)				
General and administrative	$ 14,984	$ 11,636	$ 3,348	29%

General and administrative expenses for the year ended December 31, 2011 increased by $3.3 million from the year ended December 31, 2010. The increase was primarily due to increased consulting fees of $2.1 million and increased salary and employee-related costs of $1.6 million, offset by certain cost reductions of ($0.4) million. The increased general and administrative activity was related to increased support for clinical studies.

We expect our general and administrative expenses to increase moderately to support increased activity in clinical studies.

Other Income (Expense). Other income (expense) during the years ended December 31, 2011 and 2010 were as follows:

	Year ended December 31,			
	2011	2010	Change	
($ in thousands)				
Other income, net	$ 39	$ 765	$ (726)	-95%
Change in fair value of warrants	7,583	(8,889)	$ 16,472	-185%
Total	$ 7,622	$ (8,124)	$ 15,746	

The increase in other income (expense) from the year ended December 31, 2011 compared to the year ended December 31, 2010 was due primarily to the change in the fair value of liability-classified warrants, which

50

Table of Contents

yielded a gain of $7,583 thousand in 2011 as compared to a loss of $8,889 thousand in 2010. The change in liability-classified warrants is attributable to the decrease in our stock price, decrease in remaining term and a decrease in volatility. Additional changes are attributable to increased state tax refunds and decreased interest rates on invested funds.

Liquidity and Capital Resources

As of December 31, 2012, we had approximately $73.3 million in cash and cash equivalents, compared to $104.7 million in cash and cash equivalents as of December 31, 2011. We anticipate that our cash resources will be sufficient to fund our operations into the second half of 2013. As a result, our independent registered public accounting firm has expressed a substantial doubt about our ability to continue as a going concern in their report on our financial statements. The results from the Company s PICASSO 3 pivotal trial in first-line STS are expected in the last week of March 2013. The Company has various dilutive and non-dilutive funding alternatives if the results are positive. If the results are negative, alternative cost-cutting efficiencies are planned in an attempt to extend our cash resources as long as possible, though there are no assurances that such efforts, if necessary, would be realized. In addition, changes may occur that would consume our existing capital prior to the second half of 2013, including expansion of the scope of, 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 have estimated the sufficiency of our cash resources based in part on the trial design for our PICASSO 3 pivotal trial in first-line STS and our adaptive Phase 3 trial in first-line SCLC for IV palifosfamide and our current timing expectations for the results of the PICASSO 3 pivotal trial and enrollment in our adaptive Phase 3 trial in first-line SCLC for IV palifosfamide, which may change based on the progression of enrollment. We also assumed responsibility for the advancement of two product candidates in the clinic under our Channel Agreement 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.

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 will continue to add, headcount to support our exclusive channel partnership endeavors, which will add to our general and administrative expenses going forward.

In addition to these factors, our actual cash requirements may vary materially from our current expectations for a number of other factors that may include, but are not limited to, changes in the focus and direction of our development programs, competitive and technical advances, costs associated with the development of our product candidates, our ability to secure partnering arrangements, and costs of filing, prosecuting, defending and enforcing our intellectual property rights. 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 expect that we will need additional financing to support our long-term plans for clinical trials and new product development. We expect to finance our cash needs through the sale of equity securities, strategic collaborations and/or debt financings, or through other sources that may be dilutive to existing stockholders. There can be no assurance that we will be able to obtain funding from any of these sources or, if obtained, what the terms of such funding(s) may be, or that any amount that we are able to obtain will be adequate to support our working capital requirements until we achieve profitable operations. We have no current committed sources of additional capital. Recently, capital markets have experienced a period of instability that may severely hinder our ability to raise capital within the time periods needed or on terms we consider acceptable, if at all. If we are

Table of Contents

unable to raise additional funds when needed, we may not be able to continue development and regulatory approval of our products, or we could be required to delay, scale back or eliminate some or all our research and development programs.

Recent Financing Transactions

January 2012 Public Offering

On January 20, 2012, we entered into an underwriting agreement with J. P. Morgan Securities LLC, as representative of the several underwriters named therein, relating to the issuance and sale of 9,650,000 shares of our common stock. The price to the public in the offering was $5.20 per share, and the underwriters agreed to purchase the shares from us pursuant to the underwriting agreement at a purchase price of $4.888 per share. Under the terms of the underwriting agreement, we also granted the underwriters an option, exercisable for 30 days, to purchase up to an additional 1,447,500 shares of common stock at a purchase price of $4.888 per share. The offering was made pursuant to our effective registration statement on Form S-3 (Registration Statement No. 333-177793) previously filed with the SEC, and a prospectus supplement thereunder. The underwriters purchased the 9,650,000 shares on January 25, 2012 and purchased an additional 464,401 shares on January 31, 2012 pursuant to the partial exercise of their option to purchase additional shares, resulting in our issuing a total of 10,114,401 shares. The net proceeds from the offering were approximately $49.2 million after deducting underwriting discounts and estimated offering expenses payable by us.

Cash Increases and (Decreases)

The following table summarizes our net increase (decrease) in cash and cash equivalents for the years ended December 31, 2012, 2011 and 2010 and the period from September 9, 2003 (date of inception) through December 31, 2012:

	Year ended December 31,			Period from September 9, 2003 (date of inception) through December 31, 2012
($ in thousands)	**2012**	**2011**	**2010**	
Net cash provided by (used in):				
Operating activities	$ (78,832)	$ (38,835)	$ (19,694)	$ (221,640)
Investing activities	(1,559)	(1,156)	(186)	(4,625)
Financing activities	48,984	84,312	31,433	299,571
Net increase (decrease) in cash and cash equivalents	$ (31,407)	$ 44,321	$ 11,553	$ 73,306

Net cash used in operating activities was $78.8 million for the year ended December 31, 2012 compared to $38.8 million for the year ended December 31, 2011. The $40.0 million increase was due to an increase in prepaid expenses and other current assets attributable to a related party prepayment (see Note 7 to the financial statements, Related Party Transactions), as well as an increase in the net loss from operations, caused by increased research and development activities, excluding non-cash expenses of the change in fair value of warrants, stock-based compensation, and in process research and development. Net cash used in operating activities was $38.8 million for the year ended December 31, 2011 compared to $19.7 million for the year ended December 31, 2010. The $19.1 million increase was primarily due to an increase in the net loss from operations, caused by increased research and development activities relating to the palifosfamide pivotal trial.

Net cash used in investing activities was $1.6 million for the year ended December 31, 2012 compared to $1.2 million for the year ended December 31, 2011. The increase was due to the build out of additional space in our Boston and New York offices including leasehold improvements and furniture and fixtures along with software additions.

Net cash provided by financing activities was $49.0 million for the year ended December 31, 2012 compared to $84.3 million for the year ended December 31, 2011 and $31.4 million for the year ended December 31, 2010.

52

Table of Contents

The change is primarily attributable to a $49.2 million financing that occurred during the year ended December 31, 2012 versus a $71.2 million financing and warrant exercises of $12.3 million that occurred during the year ended December 31, 2011. There was also a $32.8 million financing during the year ended December 31, 2010.

Operating capital and capital expenditure requirements

We anticipate that losses will continue for the foreseeable future. At December 31, 2012, our accumulated deficit was approximately $283.7 million. Our actual cash requirements may vary materially from those planned because of a number of factors including:

- Changes in the focus, direction and pace of our development programs;
- Competitive and technical advances;
- Costs associated with the development of our product candidates;
- Our ability to secure partnering arrangements;
- Costs of filing, prosecuting, defending and enforcing any patent claims and any other intellectual property rights, or other developments, and
- Other matters identified under Part II Item 1A. Risk Factors .

Working capital as of December 31, 2012 was $61.4 million, consisting of $80.3 million in current assets and $18.9 million in current liabilities. Working capital as of December 31, 2011 was $92.7 million, consisting of $106.1 million in current assets and $13.4 million in current liabilities.

Contractual obligations

The following table summarizes our outstanding obligations as of December 31, 2012 and the effect those obligations are expected to have on our liquidity and cash flows in future periods:

($ in thousands)	Total	Less than 1 year	2 - 3 years	4 - 5 years	More than 5 years
Operating leases	$ 5,567	$ 1,200	$ 2,445	$ 1,498	$ 424
Royalty and license fees	1,400	275	550	550	25
Contract milestone payments	25,162	17,579	7,279	304	
Total	$ 32,129	$ 19,054	$ 10,274	$ 2,352	$ 449

Our commitments for operating leases relate to the lease for our corporate headquarters in New York, New York, our operations center in Boston, Massachusetts and our office in Germantown, MD, which was closed on July 16, 2012. Our commitments for royalty and license fees relate to our patent agreement with Baxter Healthcare Corporation and our royalty agreements with Southern Research Institute and Baxter Healthcare Corporation requiring minimum royalty payments. The contract milestone payments relate to our CRO agreements with PPD Development, L.P., Pharmaceutical Research Associates, Inc., and Novella Clinical, Inc. The timing of the remaining contract milestone payments are dependent upon factors that are beyond our control, including our ability to recruit patients, the outcome of future clinical trials and any requirements imposed on our clinical trials by regulatory agencies. However, for the purpose of the above table, we have assumed that

the payment of the milestones will occur within five years of December 31, 2012 (see Note 8 to the financial statements, Commitments and Contingencies).

Critical Accounting Policies and Significant Estimates

Our management s discussion and analysis of our financial condition and results of operations is based upon our financial statements, which have been prepared in accordance with accounting principles generally accepted in

Table of Contents

the United States. The preparation of these financial statements requires us to make estimates and assumptions that affect the reported amounts of assets and liabilities and the disclosure of contingent assets and liabilities at the date of the financial statements as well as the reported expenses during the reporting periods. We evaluate our estimates and judgments on an ongoing basis. Actual results may differ materially from these estimates under different assumptions or conditions.

We believe the following are our more significant estimates and judgments used in the preparation of our financial statements:

- Clinical trial expenses;
- Fair value measurements of stock based compensation and warrants; and
- Income taxes.

Clinical Trial Expenses

Clinical trial expenses include expenses associated with CROs. The invoicing from CROs for services rendered can lag several months. We accrue the cost of services rendered in connection with CRO activities based on our estimate of site management, monitoring costs, and project management costs. We maintain regular communication with our CROs to gauge the reasonableness of our estimates. Differences between actual clinical trial expenses and estimated clinical trial expenses recorded have not been material and are adjusted for in the period in which they become known.

Fair Value Measurements of Stock Based Compensation and Warrants

Accounting standards define fair value, establish a framework for measuring fair value under generally accepted accounting principles and enhance disclosures about fair value measurements. Fair value is defined as the exchange price that would be received for an asset or paid to transfer a liability (an exit price) in the principal or most advantageous market for the asset or liability in an orderly transaction between market participants on the measurement date. Valuation techniques used to measure fair value must maximize the use of observable inputs and minimize the use of unobservable inputs. The standard describes a fair value hierarchy based on three levels of inputs, of which the first two are considered observable and the last unobservable, that may be used to measure fair value which are the following:

- Level 1 Quoted prices in active markets for identical assets or liabilities.
- Level 2 Inputs other than Level 1 that are observable, either directly or indirectly, such as quoted prices for similar assets or liabilities; quoted prices in markets that are not active; or other inputs that are observable or can be corroborated by observable market data for substantially the full term of the assets or liabilities.
- Level 3 Unobservable inputs that are supported by little or no market activity and that are significant to the fair value of the assets or liabilities.

We make certain assumptions in order to value and expense our share-based compensation awards and liability classified warrants. In connection with valuing stock options and liability classified warrants we use the Black-Scholes model and the binomial model, respectively, which require us to estimate certain subjective assumptions. The key assumptions we make are: the expected volatility of our stock; the expected term of the award; and the expected forfeiture rate related to share based awards. In connection with our restricted stock programs, we make assumptions principally related to the forfeiture rate. The key assumptions used to estimate fair value for our warrants include current and expected stock prices, volatility, dividends, forward yield curves and discount rates.

We review our valuation assumptions periodically and, as a result, we may change our valuation assumptions used to value share-based awards granted in future periods and warrants. Such changes may lead to a significant change in the expense we recognize in connection with

share-based payments and warrants.

Table of Contents

Income Taxes

In preparing our financial statements, we estimate our income tax liability in each of the jurisdictions in which we operate by estimating our actual current tax expense together with assessing temporary differences resulting from differing treatment of items for tax and financial reporting purposes. These differences result in deferred tax assets and liabilities, which, prior to the consideration for the need for a valuation allowance, are included on the balance sheet. Significant management judgment is required in assessing the realizability of our deferred tax assets. In performing this assessment, we consider whether it is more likely than not that some portion or all of the deferred tax assets will not be realized. The ultimate realization of deferred tax assets is dependent upon the generation of future taxable income during the periods in which those temporary differences become deductible. In making this determination, under the applicable financial accounting standards, we are allowed to consider the scheduled reversal of deferred tax liabilities, projected future taxable income, and the effects of tax planning strategies. Our estimates of future taxable income include, among other items, our estimates of future income tax deductions related to the exercise of stock options. In the event that actual results differ from our estimates, we adjust our estimates in future periods and we may need to establish a valuation allowance, which could materially impact our financial position and results of operations.

We account for uncertain tax positions using a more-likely-than-not threshold for recognizing and resolving uncertain tax positions. The evaluation of uncertain tax positions is based on factors that include, but are not limited to, changes in tax law, the measurement of tax positions taken or expected to be taken in tax returns, the effective settlement of matters subject to audit, new audit activity and changes in facts or circumstances related to a tax position. We evaluate uncertain tax positions on an annual basis and adjust the level of the liability to reflect any subsequent changes in the relevant facts surrounding the uncertain positions. Our liabilities for uncertain tax positions can be relieved only if the contingency becomes legally extinguished through either payment to the taxing authority or the expiration of the statute of limitations, the recognition of the benefits associated with the position meet the more-likely-than-not threshold or the liability becomes effectively settled through the examination process. We consider matters to be effectively settled once the taxing authority has completed all of its required or expected examination procedures, including all appeals and administrative reviews; we have no plans to appeal or litigate any aspect of the tax position; and we believe that it is highly unlikely that the taxing authority would examine or re-examine the related tax position. We also accrue for potential interest and penalties, related to unrecognized tax benefits in income tax expense.

Recent Accounting Pronouncements

In January 2011, we adopted Accounting Standards Update, or ASU No. 2010-06, *Improving Disclosures About Fair Value Measurements* which requires additional disclosure about the amounts of and reasons for significant transfers in and out of Level 1 and Level 2 fair value measurements. In addition, effective for interim and annual periods beginning after December 15, 2010, this standard further requires an entity to present disaggregated information about activity in Level 3 fair value measurements on a gross basis, rather than as one net amount. As this accounting standard only requires enhanced disclosure, the adoption of this newly issued accounting standard did not impact our financial position or results of operations.

In May 2011, the Financial Accounting Standards Board, or FASB, issued ASU No. 2011-04, *Fair Value Measurement (Topic 820): Amendments to Achieve Common Fair Value Measurement and Disclosure Requirements in U.S. GAAP and IFRSs* . This newly issued accounting standard clarifies the application of certain existing fair value measurement guidance and expands the disclosures for fair value measurements that are estimated using significant unobservable (Level 3) inputs. This ASU is effective on a prospective basis for annual and interim reporting periods beginning on or after December 15, 2011, which for us is January 1, 2012. The adoption of this standard did not have a material impact on our financial position or results of operations.

In June 2011, the FASB issued ASU No. 2011-05, *Comprehensive Income (Topic 220) Presentation of Comprehensive Income*. This newly issued accounting standard (1) eliminates the option to present the components of other comprehensive income as part of the statement of changes in stockholders equity;

Table of Contents

(2) requires the consecutive presentation of the statement of net income and other comprehensive income; and (3) requires an entity to present reclassification adjustments on the face of the financial statements from other comprehensive income to net income. The amendments in this ASU do not change the items that must be reported in other comprehensive income or when an item of other comprehensive income must be reclassified to net income nor do the amendments affect how earnings per share is calculated or presented. This ASU is required to be applied retrospectively and is effective for fiscal years and interim periods within those years beginning after December 15, 2011. As this accounting standard only requires enhanced disclosure, the adoption of this standard did not impact our financial position or results of operations.

In December 2011, the FASB issued Accounting Standards Update, or ASU, No. 2011-11 *Balance Sheet (Topic 210): Disclosures About Offsetting Assets and Liabilities* which requires an entity to disclose information about offsetting and related arrangements to enable users of its financial statements to understand the effect of those arrangements on its financial position. This update is effective for periods beginning after January 1, 2013. The adoption of this standard will not have an impact on our financial position or results of operations.

Off-Balance Sheet Arrangements

We currently do not have any special purpose entities or off-balance sheet financing arrangements.

Item 7A. Quantitative and Qualitative Disclosures About Market Risk

Our exposure to market risk is limited to our cash. The goals of our investment policy are preservation of capital, fulfillment of liquidity needs and fiduciary control of cash and investments. We also seek to maximize income from our investments without assuming significant risk. To achieve our goals, we maintain our cash in interest-bearing cash accounts. As all of our investments are cash deposits in a global bank, it is subject to minimal interest rate risk.

Effect of Currency Exchange Rates and Exchange Rate Risk Management

We conduct clinical studies outside of the United States primarily in Western Europe. These business operations are not material at this time, therefore any currency fluctuations will not have a material impact on our financial position, results of operations or cash flows.

Item 8. Financial Statements and Supplementary Data

The information required by this Item 8 is contained on pages F-1 through F-45 of this annual report on Form 10-K and is incorporated herein by reference.

Item 9. Changes in and Disagreements with Accountants on Accounting and Financial Disclosures

None.

Item 9A. Controls and Procedures

Evaluation of Disclosure Controls and Procedures.

Under the supervision and with the participation of our management, including our Chief Executive Officer and Chief Financial Officer, we have evaluated the effectiveness of our disclosure controls and procedures, as such term is defined under Rule 13a-15(e) or 15d-15(e) promulgated under the Exchange Act, as of December 31, 2012. Based on that evaluation, our Chief Executive Officer and Chief Financial Officer have concluded that as of such date, our disclosure controls and procedures were effective.

Management s Report on Internal Control over Financial Reporting

Our management is responsible for establishing and maintaining adequate internal control over financial reporting for us. Internal control over financial reporting (as defined in Rule 13a-15(f) of the Exchange Act) is a

Table of Contents

process to provide reasonable assurance regarding the reliability of our financial reporting for external purposes in accordance with accounting principles generally accepted in the United States of America. Internal control over financial reporting includes maintaining records that in reasonable detail accurately and fairly reflect our transactions; providing reasonable assurance that transactions are recorded as necessary for preparation of our financial statements; providing reasonable assurance that receipts and expenditures of company assets are made in accordance with management authorization; and providing reasonable assurance that unauthorized acquisition, use or disposition of company assets that could have a material effect on our financial statements would be prevented or detected on a timely basis. Because of its inherent limitations, internal control over financial reporting is not intended to provide absolute assurance that a misstatement of our financial statements would be prevented or detected.

Management conducted an evaluation of the effectiveness, as of December 31, 2012, of our internal control over financial reporting based on the framework in *Internal Control Integrated Framework* issued by the Committee of Sponsoring Organizations of the Treadway Commission. Based on this evaluation, management concluded that our internal control over financial reporting was effective as of December 31, 2012.

McGladrey LLP, an independent registered public accounting firm, has issued an attestation report on our internal control over financial reporting as of December 31, 2012. That report is included in this annual report on Form 10-K.

Changes in Internal Controls over Financial Reporting

There were no changes in our internal control over financial reporting during the quarter ended December 31, 2012 that have materially affected, or are reasonably likely to materially affect, our internal control over financial reporting.

Item 9B. Other Information

None.

Table of Contents

PART III

Item 10. Directors, Executive Officers and Corporate Governance

Information in response to this Item is incorporated herein by reference from the information in our definitive proxy statement to be filed pursuant to Regulation 14A within 120 days after the end of the fiscal year covered by this annual report on Form 10-K under the sections entitled *Proposals Election of Directors, Executive Officers, Information Regarding the Board of Directors and Corporate Governance* and *Stock Ownership*.

Item 11. Executive Compensation

Information in response to this Item is incorporated herein by reference from the information in our definitive proxy statement to be filed pursuant to Regulation 14A within 120 days after the end of the fiscal year covered by this annual report on Form 10-K under the section entitled *Executive Compensation*.

Item 12. Security Ownership of Certain Beneficial Owners and Management and Related Stockholder Matters

Securities Authorized for Issuance under Equity Compensation Plans

Our Amended and Restated 2003 Stock Option Plan, or the 2003 Plan, and our 2012 Stock Option Plan, or the 2012 Plan, are our only equity compensation plans approved by our stockholders. The following table sets forth certain information as of December 31, 2012 with respect to the 2003 and 2012 Plans:

Plan Category	Number of Securities to be Issued Upon Exercise of Outstanding Options (A)	Weighted-Average Exercise Price of Outstanding Options (B)	Number of Securities Remaining Available for Future Issuance Under Equity Compensation Plans (Excluding Securities Reflected in Column (A)) (C)
Equity compensation plans approved by stockholders:			
2003 Stock Option Plan	5,608,855	$ 4.03	
2012 Stock Option Plan	2,293,980	$ 4.34	1,706,020
Total:	7,902,835	$ 4.12	1,706,020
Equity compensation plans not approved by stockholders:			
		$	
Total:		$	

Additional information in response to this Item is incorporated herein by reference from the information in our definitive proxy statement to be filed pursuant to Regulation 14A within 120 days after the end of the fiscal year covered by this annual report on Form 10-K under the section entitled *Stock Ownership*.

Item 13. Certain Relationships and Related Transactions, and Director Independence

Information in response to this Item is incorporated herein by reference from the information in our definitive proxy statement to be filed pursuant to Regulation 14A within 120 days after the end of the fiscal year covered by this annual report on Form 10-K under the section entitled *Certain Relationships and Related Transactions and Information Regarding the Board of Directors and Corporate Governance*.

Item 14. Principal Accountant Fees and Services

Information in response to this Item is incorporated herein by reference from the information in our definitive proxy statement to be filed pursuant to Regulation 14A within 120 days after the end of the fiscal year covered by this annual report on Form 10-K under the section entitled *Independent Registered Public Accounting Firm Fees and Other Matters*.

Table of Contents

PART IV

Item 15. Exhibits, Financial Statement Schedules

(1) Financial Statements:

The Financial Statements required to be filed by Item 8 of this annual report on Form 10-K, and filed in this Item 15, are as follows: