

CTI BIOPHARMA CORP
Form 10-K
March 12, 2015

UNITED STATES

SECURITIES AND EXCHANGE COMMISSION

Washington, D.C. 20549

FORM 10-K

(Mark One)

☒ ANNUAL REPORT PURSUANT TO SECTION 13 OR 15(d) OF THE SECURITIES EXCHANGE ACT OF 1934
For the fiscal year ended December 31, 2014

OR

☐ TRANSITION REPORT PURSUANT TO SECTION 13 OR 15(d) OF THE SECURITIES EXCHANGE ACT OF 1934

For the transition period from _____ to _____

Commission file number: 001-12465

CTI BIOPHARMA CORP.

(Exact name of registrant as specified in its charter)

Washington	91-1533912
(State or other jurisdiction of incorporation or organization)	(I.R.S. Employer Identification Number)

3101 Western Avenue, Suite 600

Seattle, WA	98121
(Address of principal executive offices)	(Zip Code)

Registrant's telephone number, including area code: (206) 282-7100

Securities registered pursuant to Section 12(b) of the Act:

Title of each class	Name of each exchange on which registered
Common Stock, no par value	The NASDAQ Stock Market LLC

Securities registered pursuant to Section 12(g) of the Act:

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Preferred Stock Purchase Rights

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

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

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

Indicate by check mark whether the registrant has submitted electronically and posted on its corporate Web site, if any, every Interactive Data File required to be submitted and posted pursuant to Rule 405 of Regulation S-T (§232.405 of this chapter) during the preceding 12 months (or for such shorter period that the registrant was required to submit and post such files). Yes ☒ No ☐

Indicate by check mark if disclosure of delinquent filers pursuant to Item 405 of Regulation S-K (§229.405 of this chapter) is not contained herein, and will not be contained, to the best of the 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, or a non-accelerated filer, or a smaller reporting company. See the definitions of "large accelerated filer," "accelerated filer" and "smaller reporting company" in Rule 12b-2 of the Exchange Act. (Check one):

Large accelerated filer ☐

Accelerated filer ☒

Non-accelerated filer ☐ (Do not check if a smaller reporting company) 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 ☒

As of June 30, 2014, the aggregate market value of the registrant's common equity held by non-affiliates was \$330,945,510. Shares of common stock held by each executive officer and director and by each person known to the registrant who beneficially owns more than 5% of the outstanding shares of the registrant's common stock have been excluded in that such persons may under certain circumstances be deemed to be affiliates. This determination of executive officer or affiliate status is not necessarily a conclusive determination for other purposes. The registrant has no non-voting common stock outstanding.

The number of outstanding shares of the registrant's common stock as of March 5, 2015 was 180,255,852.

DOCUMENTS INCORPORATED BY REFERENCE

Portions of the registrant's definitive proxy statement relating to its 2015 annual meeting of shareholders, or the 2015 Proxy Statement, are incorporated by reference into Part III of this Annual Report on Form 10-K where indicated. The 2015 Proxy Statement will be filed with the U.S. Securities and Exchange Commission within 120 days after the end of the fiscal year to which this report relates.

CTI BIOPHARMA CORP.

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Forward Looking Statements

This Annual Report on Form 10-K and the documents we incorporate by reference herein or therein may contain “forward-looking statements” within the meaning of the United States, or the U.S., federal securities laws. All statements other than statements of historical fact are forward-looking statements, including, without limitation:

- any statements regarding future operations, plans, expectations, intentions, regulatory filings or approvals;
- any statements regarding the performance, or likely performance, outcomes or economic benefit of any licensing collaboration or other arrangement;
- any projections of revenues, operating expenses or other financial terms, and any projections of cash resources, including regarding our potential receipt of future milestone payments under any of our agreements with third parties and expected sales of PIXUVRI;
- any statements of the plans and objectives of management for future operations or programs;
- any statements concerning proposed new products;
- any statements regarding the safety and efficacy or future availability of any of our compounds;
- any statements on plans regarding proposed or potential clinical trials or new drug filing strategies, timelines or submissions;
- any significant disruptions in our information technology systems;
- any statements regarding compliance with the listing standards of The NASDAQ Stock Market and the Mercato Telematico Azionario, or the MTA, in Italy;
- any statements regarding potential future partnerships, licensing arrangements, mergers, acquisitions or other transactions;
- any statements regarding future economic conditions or performance; and
- any statements of assumption underlying any of the foregoing.

In some cases, forward-looking statements can be identified by terms such as “anticipates,” “believes,” “continue,” “could,” “estimates,” “expects,” “intends,” “may,” “plans,” “potential,” “predicts,” “projects,” “should” or “will” or the negative thereof and similar expressions. Such statements are based on management’s current expectations and are subject to risks and uncertainties, which may cause actual results to differ materially from those set forth in the forward-looking statements. In particular, this Annual Report on Form 10-K addresses top line results regarding primary endpoints of the PERSIST-1 study, and should be evaluated together with secondary endpoints, safety and additional data once such data has been more fully analyzed and is made publicly available. The statements are based on assumptions about many important factors and information currently available to us to the extent we have thus far had an opportunity to fully and carefully evaluate such information in light of all surrounding facts, circumstances, recommendations and analyses. There can be no assurance that such expectations or any of the forward-looking statements will prove to be correct, and actual results could differ materially from those projected or assumed in the forward-looking statements. We urge you to carefully review the disclosures we make concerning risks and other factors that may affect our business and operating results, including those made under Part I, Item 1, “Business,” Part I, Item 1A, “Risk Factors,” Part II, Item 7, “Management’s Discussion and Analysis of Financial Condition and Results of Operations,” and elsewhere in this Annual Report on Form 10-K and any risk factors contained in subsequent Quarterly Reports on Form 10-Q that we file with the Securities and Exchange Commission, or the SEC.

We do not intend to update any of the forward-looking statements after the date of this Annual Report on Form 10-K to conform these statements to actual results or changes in our expectations. Readers are cautioned not to place undue reliance on these forward-looking statements, which apply only as of the date of this Annual Report on Form 10-K.

In this Annual Report on Form 10-K, all references to “we,” “us,” “our,” the “Company” and “CTI” mean CTI BioPharma Co. and our subsidiaries, except where it is otherwise made clear.

PART I

Item 1. Business

Overview

We are a biopharmaceutical company focused on the acquisition, development and commercialization of novel targeted therapies covering a spectrum of blood-related cancers that offer a unique benefit to patients and healthcare providers. Our goal is to build a profitable company by generating income from products we develop and commercialize, either alone or with partners. We are currently concentrating our efforts on treatments that target blood-related cancers where there is an unmet medical need. In particular, we are primarily focused on commercializing PIXUVRI[®] (pixantrone), or PIXUVRI, in the European Union, or the E.U., for the treatment of adult patients with multiply relapsed or refractory aggressive B-cell non-Hodgkin lymphoma, or NHL, and conducting a Phase 3 clinical trial program of pacritinib for the treatment of adult patients with myelofibrosis to support regulatory submission for approval in the U.S. and Europe. We are also evaluating pacritinib in earlier clinical trials as treatment for other blood-related cancers.

PIXUVRI

PIXUVRI is a novel aza-anthracenedione with unique structural and physiochemical properties. In May 2012, the European Commission granted conditional marketing authorization in the E.U. for PIXUVRI as a monotherapy for the treatment of adult patients with multiply relapsed or refractory aggressive B-cell NHL. PIXUVRI is the first approved treatment in the E.U. for patients with multiply relapsed or refractory aggressive B-cell NHL who have failed two or three prior lines of therapy. As part of the conditional marketing authorization, we are required to conduct a post-authorization trial, or PIX306, which compares PIXUVRI and rituximab with gemcitabine and rituximab in the setting of aggressive B-cell NHL.

PIXUVRI is currently available in Austria, Denmark, Finland, France, Germany, Israel, Italy, Netherlands, Norway, Sweden and the United Kingdom, or the U.K., and has achieved reimbursement decisions under varying conditions in England/Wales, Italy, France, Germany, the Netherlands and Spain. In almost all European markets, pricing and availability of prescription pharmaceuticals are subject to governmental control. Decisions by governmental authorities will impact the price and market acceptance of PIXUVRI. Accordingly, any future revenues are dependent on market acceptance of PIXUVRI, the reimbursement decisions made by the governmental authorities in each country where PIXUVRI is available for sale and other factors. Although we do not have and are not currently pursuing regulatory approval of PIXUVRI in the U.S., we may reevaluate a possible submission strategy in the U.S. based on the data generated from the PIX306 study.

We have established a commercial organization, including sales, marketing, supply chain management and reimbursement capabilities, to commercialize PIXUVRI in certain countries in the E.U. In September 2014, we entered into an exclusive license and collaboration agreement, or the Servier Agreement, with Les Laboratoires Servier and Institut de Recherches Internationales Servier, or collectively, Servier, with respect to the development and commercialization of PIXUVRI. Under the Servier Agreement, we retain full commercialization rights to PIXUVRI in Austria, Denmark, Finland, Germany, Israel, Norway, Sweden, Turkey, the U.K. and the U.S., while Servier has exclusive rights to commercialize PIXUVRI in all other countries. We received an upfront payment from Servier of €14.0 million (or \$17.8 million using the currency exchange rate as of the date we received the funds in October 2014), and we have the potential to receive milestone payments under the Servier Agreement of up to €89.0 million. For additional information on our collaboration with Servier, please see the discussion in Part I, Item 1, “Business – License Agreements and Additional Milestone Activities – Servier”.

Pacritinib

Our lead development candidate, pacritinib, is an oral multikinase inhibitor with activity against Janus Kinase 2, or JAK2, and FMS-like tyrosine kinase, or FLT3, as well as other kinases, and is currently being evaluated in adult patients with myelofibrosis. Myelofibrosis is a blood-related cancer caused by the accumulation of malignant bone marrow cells that triggers an inflammatory response, scarring the bone marrow and limiting its ability to produce red blood cells prompting the spleen and liver to take over this function. Symptoms that arise from this disease include enlargement of the spleen, anemia, extreme fatigue, itching and pain. We believe pacritinib may offer an advantage over other JAK inhibitors through effective treatment of symptoms while having less treatment-emergent thrombocytopenia and anemia than has been seen in the currently approved JAK inhibitor.

In collaboration with Baxter International, Inc., or Baxter, pursuant to our worldwide license agreement to develop and commercialize pacritinib, or the Baxter Agreement, we are pursuing a broad approach to advancing pacritinib for adult patients with myelofibrosis by conducting two Phase 3 clinical trials: one in a broad set of patients without limitations on blood platelet counts, the PERSIST-1 trial; and the other in patients with low platelet counts, the PERSIST-2 trial. In October 2013, we reached an agreement with the U.S. Food and Drug Administration, or the FDA, on a Special Protocol Assessment, or SPA, for PERSIST-2.

In August 2014, pacritinib was granted Fast Track designation by the FDA for the treatment of intermediate and high risk myelofibrosis, including, but not limited, to patients with disease-related thrombocytopenia, patients experiencing treatment-emergent thrombocytopenia on other JAK2 therapy or patients who are intolerant of, or whose symptoms are sub-optimally managed on, other JAK2 therapy. The FDA's Fast Track process is designed to facilitate the development and expedite the review of drugs to treat serious conditions and fill an unmet medical need. The PERSIST-1 and PERSIST-2 clinical trials are intended to support a potential regulatory submission to the FDA or the European Medicines Agency, or the EMA.

In March 2015, we reported top-line results for the primary endpoint from PERSIST-1 for the treatment of adult patients with myelofibrosis. The primary endpoint of the trial was the proportion of patients achieving a 35 percent or greater reduction in spleen volume from baseline to Week 24 as measured by magnetic resonance imaging, or MRI, or computerized tomography, or CT, when compared with physician-specified best available therapy, excluding treatment with JAK2 inhibitors. The trial met its primary endpoint in the intent-to-treat population with statistically significant activity observed in patients irrespective of their initial platelet count, including patients with very low platelet counts at study entry. For additional information concerning the top-line results, see Part I, Item 1, "Business—Development Candidates—Pacritinib—Development in Myelofibrosis".

Under the Baxter Agreement, we share joint commercialization rights to pacritinib with Baxter in the U.S., while Baxter has exclusive commercialization rights for all indications outside the U.S. In connection with the execution of the Baxter Agreement, we received a \$60 million upfront payment, which included an equity investment of \$30 million, and we have the potential to receive \$302 million in clinical, regulatory, commercial launch and sales milestones. Of these milestones, we have received a \$20 million development milestone payment in connection with the first treatment dosing of the last patient enrolled in PERSIST-1. Additionally, we will share any U.S. profits from pacritinib equally and will receive royalties on any net sales of pacritinib in non-U.S. markets. For additional information relating to the Baxter Agreement, see Part I, Item 1, "Business—License Agreements and Additional Milestone Activities—Baxter".

Other Pipeline Candidates

Our earlier stage product candidate, tosedostat, is a novel oral, once-daily aminopeptidase inhibitor that has demonstrated significant responses in patients with acute myeloid leukemia, or AML. It is currently being evaluated in several Phase 2 cooperative group-sponsored trials and investigator-sponsored trials, or ISTs. These trials are evaluating tosedostat in combination with hypomethylating agents in AML and myelodysplastic syndrome, or MDS, which are cancers of the blood and bone marrow. We anticipate data from these signal-finding trials may be used to determine an appropriate design for a Phase 3 trial.

Although our efforts are focused on developing and commercializing treatments that target blood-related cancers, we continue to evaluate our pipeline candidate paclitaxel poliglumex, or Opaxio™, which targets solid tumors. We are evaluating this candidate through cooperative group sponsored trials and ISTs, such as the ongoing maintenance therapy trial in patients with ovarian cancer.

Our Strategy

Our objective is to become a leader in the acquisition, development and commercialization of novel therapeutics for the treatment of blood-related cancers. The key elements of our strategy to achieve these objectives are to:

- Successfully Commercialize PIXUVRI. Together with Servier, we intend to continue our efforts to build a successful PIXUVRI franchise in Europe as well as other markets. We are currently focused on educating physicians on the unmet medical need and building brand awareness for PIXUVRI among physicians in the countries where PIXUVRI is available.
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Develop Pacritinib in Myelofibrosis and Additional Indications. Together with Baxter, we intend to develop and commercialize pacritinib for adult patients with myelofibrosis. We also intend to continue evaluation of pacritinib in other blood-related cancers, including AML and MDS, through ongoing and planned ISTs.

·Continue to Develop our Other Pipeline Programs. We believe that it is important to maintain a diverse pipeline to sustain our future growth. To accomplish this, we intend to continue to advance the development of our other pipeline candidates through cooperative group sponsored trials and ISTs. Sponsoring such trials provides us with a more economical approach for further developing our investigational products.

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· Evaluate Strategic Product Collaborations to Accelerate Development and Commercialization. Where we believe it may be beneficial, we intend to evaluate additional collaborations to broaden and accelerate clinical trial development and potential commercialization of our product candidates. Collaborations have the potential to generate non-equity based operating capital, supplement our own internal expertise and provide us with access to the marketing, sales and distribution capabilities of our collaborators in specific territories.

· Identify and Acquire Additional Pipeline Opportunities. Our current pipeline is the result of licensing and acquiring assets that we believe were initially undervalued opportunities. We plan to continue to seek out additional product candidates in an opportunistic manner.

Product and Development Portfolio

The following table summarizes our current product and development portfolio:

	Indications/Intended Use	Status
PIXUVRI (pixantrone)	Multiply relapsed aggressive B-cell NHL	Conditional Marketing Authorization—Marketed in E.U.
	Aggressive NHL, 2 nd line >1 relapse, combination with rituximab (PIX306) post-approval study	Phase 3 ongoing
Pacritinib	Myelofibrosis, PERSIST-1, All platelet levels(2)	Phase 3 ongoing, Enrollment completed, Top-line results
	Myelofibrosis, PERSIST-2, Platelet counts ≤100,000/μL	Phase 3 ongoing
	Relapsed AML(1)	Phase 2 ongoing
	MDS(1)	Phase 2 initiating
	Front-line AML(1)	Phase 2 ongoing
Tosedostat	AML/MDS(1)	Phase 2 ongoing
Opaxio	Ovarian cancer, maintenance(1)(2)	Phase 3 ongoing

- (1) We support the development of these investigational agents through cooperative group sponsored trials and ISTs.
- (2) These trials have completed enrollment and the patients are being followed.

Oncology Market Overview and Opportunity

According to the American Cancer Society, or ACS, cancer is the second leading cause of death in the U.S., resulting in close to 589,430 deaths annually, or more than 1,620 people per day. Approximately 1.7 million new cases of cancer were expected to be diagnosed in 2015 in the U.S. The most commonly used methods for treating patients with cancer are surgery, radiation and chemotherapy. Patients usually receive a combination of these treatments depending upon the type and extent of their disease.

We believe our expertise in blood-related cancers, together with our ability to identify unique therapies that address unmet medical needs that are potentially less toxic and more effective at treating and curing patients, fills a significant unmet medical need for cancer patients.

Commercialized Product

PIXUVRI

Overview

Anthracyclines are one of the most potent classes of anti-cancer agents used in first-line treatment of aggressive NHL, leukemia and breast cancer. For these diseases, anthracycline-containing regimens can often produce long-term cancer remissions and cures. However, the currently-marketed anthracyclines can cause severe, permanent and life-threatening cardiac toxicity when administered beyond widely-recognized cumulative lifetime doses. This toxicity often prevents repeat use of anthracyclines in patients who relapse after first-line anthracycline treatment. In addition, the cardiotoxicity of anthracyclines prevents their use in combination with other drugs that can also cause cardiac toxicity. As a result, chemotherapy regimens that do not include anthracyclines are often used for the second-line treatment of aggressive NHL, leukemia and breast cancer.

PIXUVRI is being developed in an effort to improve the activity and safety in treating cancers often treated with the anthracycline family of anti-cancer agents. PIXUVRI is not an anthracycline but rather a novel aza-anthracenedione with unique structural and physiochemical properties. Based on its ease of administration, unique anti-tumor activity and reduced risk of cardiotoxicity, we believe PIXUVRI could gain a significant share in the relapsed aggressive NHL market. We also believe that such a drug could allow repeat therapy in relapsed patients and could allow combination therapy with a broader range of chemotherapies.

Unlike anthracyclines, PIXUVRI does not bind to cardiac topo-isomerase II beta, a major mediator of anthracycline associated cardiotoxicity. In addition, in contrast to doxorubicin, PIXUVRI does not produce toxic free oxygen radicals in cultured cardiac cells that are thought to be responsible for early anthracycline cardiotoxicity. Also unlike anthracyclines, rather than intercalating with deoxyribonucleic acid, or DNA, PIXUVRI hydrogen bonds to and alkylates DNA, thus forming stable DNA adducts with particular specificity for CpG rich, hypermethylated sites. The result is progressive disruption of mitosis and therefore killing of rapidly dividing cells like those found in many tumors. PIXUVRI appears to impair chromosomal segregation during mitosis, thereby generating loss of genetic material in daughter cells, an abnormality, which is ultimately lethal to tumor cells. These novel pharmacologic differences may allow re-introduction of a single-agent chemotherapy drug with anthracycline-like potency in the treatment of patients who are resistant to other cytotoxic agents such as doxorubicin.

PIXUVRI for the Treatment of NHL

We are specifically developing and commercializing PIXUVRI for the treatment of aggressive NHL. NHL is caused by the abnormal proliferation of lymphocytes, which are cells key to the functioning of the immune system. NHL usually originates in lymph nodes and spreads through the lymphatic system. The ACS estimated that there would be 71,850 people diagnosed with NHL in the U.S. and approximately 19,790 people would die from this disease in 2015. The World Health Organization's International Agency for Research on Cancer's 2012 GLOBOCAN database estimates that, in the E.U., approximately 79,312 people will be diagnosed with NHL and 30,730 are estimated to die from NHL annually. NHL is the seventh most common type of cancer. NHL can be broadly classified into two main forms, each with many subtypes; aggressive NHL is a rapidly growing form of the disease that moves into advanced stages much faster than indolent NHL, which progresses more slowly.

Aggressive B-cell NHL is the most common subtype, accounting for about 55 percent of NHL cases. After initial therapy for aggressive NHL with anthracycline-based combination therapy, one-third of patients typically develop progressive disease. Approximately half of these patients are likely to be eligible for intensive second-line treatment and stem cell transplantation, although 50 percent are expected not to respond. For those patients who fail to respond or relapse following second line treatment, treatment options are limited, and usually palliative only. PIXUVRI is the first treatment approved in the E.U. for patients with multiply relapsed or refractory aggressive B-cell NHL. Neither

PIXUVRI nor any other drugs are approved for this indication in the U.S.

Clinical Trials and Conditional Marketing Approval of PIXUVRI in the E.U.

The pivotal Phase 3 trial, or PIX301, evaluated PIXUVRI for patients with relapsed or refractory aggressive B-cell NHL. The trial enrolled 140 patients randomized to receive either PIXUVRI or another single-agent drug currently used for the treatment of this patient population and selected by the physician. Twenty percent of patients in the trial who received PIXUVRI achieved a complete or unconfirmed complete response at end of treatment compared with 5.7 percent in the comparator group ($p=0.021$). Median progression-free survival, or PFS, in the intent-to-treat population was also greater with PIXUVRI than with comparators: 5.3 versus 2.6 months ($p=0.005$). PIXUVRI had predictable and manageable toxicities when administered at the proposed dose and schedule in heavily pre-treated patients. The most common (incidence greater than or equal to 10 percent) grade 3/4 adverse events reported for PIXUVRI-treated subjects across trials were neutropenia and leukopenia. Other common adverse events (any grade) included infection, anemia, thrombocytopenia, asthenia, pyrexia and cough. The PIX301 study was published in Lancet Oncology in May 2012.

In May 2012, PIXUVRI was granted conditional marketing authorization by the European Commission as a monotherapy for the treatment of adult patients with multiply relapsed or refractory aggressive NHL. The European Commission granted conditional marketing authorization for PIXUVRI based, in part, on the results of the PIX301 trial.

Similar to accelerated approval regulations in the U.S., conditional marketing authorizations can be granted in the E.U. by the European Commission in exceptional circumstances in accordance with the procedures discussed in Part I, Item 1, Business—Government Regulation—Non-U.S. Regulation. A conditional marketing authorization is required to be renewed annually. In connection with the conditional marketing authorization for PIXUVRI, we are conducting the PIX306 post-marketing study, which is an ongoing randomized, controlled Phase 3 clinical trial comparing PIXUVRI-rituximab to gemcitabine-rituximab in patients who have relapsed after one to three prior regimens for aggressive B-cell NHL and who are not eligible for autologous stem cell transplant. Under the provisions of the conditional marketing authorization for PIXUVRI, we are required to submit the clinical study report for the post-marketing study in November 2016 to further investigate the effects of using PIXUVRI in patients who had received prior treatment with rituximab. In December 2013, we obtained an agreement from the EMA to change the primary endpoint of the PIX306 study from overall survival to PFS. PIX306 is now expected to enroll approximately 220 patients versus the 350 patients previously planned and is currently enrolling patients in sites in the U.S. and Europe. If the PIX306 study is deemed successful by the applicable European regulatory authorities, it is intended that the conditional approval for PIXUVRI would no longer be necessary in the E.U. and instead a full marketing authorization would be granted by the European Commission. We believe that the data from the PIX306 study could potentially support a registration application in the U.S.

Commercialization of PIXUVRI in the E.U.

In September 2012, we initiated E.U. commercialization of PIXUVRI. PIXUVRI is currently available in Austria, Denmark, Finland, France, Germany, Israel, Italy, Netherlands, Norway, Sweden and the U.K., and has achieved reimbursement decisions under varying conditions in England/Wales, Italy, France, Germany, the Netherlands and Spain. PIXUVRI is not approved in the U.S.

We have established a commercial organization, including sales, marketing, supply chain management and reimbursement capabilities, to commercialize PIXUVRI in certain countries in the E.U., and in September 2014 we entered into the Servier Agreement with respect to the development and commercialization of PIXUVRI. Under the Servier Agreement, we retain full commercialization rights to PIXUVRI in Austria, Denmark, Finland, Germany, Israel, Norway, Sweden, Turkey, the U.K. and the U.S., while Servier has exclusive rights to commercialize PIXUVRI in all other countries. We received an upfront payment from Servier of €14.0 million (or \$17.8 million using the currency exchange rate as of the date we received the funds in October 2014), and we have the potential to receive milestone payments under the Servier Agreement of up to €89.0 million. Of the foregoing potential milestone payments, we received a €1.5 million milestone payment in February 2015 relating to the attainment of reimbursement approval for PIXUVRI in Spain. For additional information on our collaboration with Servier, please see the discussion in Part I, Item 1, “Business—License Agreements and Additional Milestone Activities—Servier”.

As discussed in Part I, Item 1, “Business—Manufacturing, Distribution and Associated Operations,” we utilize third parties for the manufacture, storage and distribution of PIXUVRI, as well as for other associated supply chain operations. Our strategy of utilizing third parties in such manner allows us to direct our resources to the development and commercialization of compounds rather than to the establishment and maintenance of facilities for such operational activities.

Development Candidates

Pacritinib

Development in Myelofibrosis

Our lead development candidate, pacritinib, is an oral multikinase inhibitor with activity against JAK2, FLT3 and other kinases. The JAK family of enzymes is a central component in signal transduction pathways, which are critical to normal blood cell growth and development as well as inflammatory cytokine expression and immune responses. Mutations in these kinases have been shown to be directly related to the development of a variety of blood-related cancers, including myeloproliferative neoplasms, leukemia and lymphoma. Pacritinib may offer an advantage over other JAK inhibitors through effective treatment of symptoms while having less treatment-emergent thrombocytopenia and anemia than has been seen in currently approved and in-development JAK inhibitors.

As part of our collaboration with Baxter, we are pursuing a broad approach to advancing pacritinib for adult patients with myelofibrosis by conducting two Phase 3 clinical trials: one in a broad set of patients without limitations on blood platelet counts, the PERSIST-1 trial; and the other in patients with low platelet counts, the PERSIST-2 trial.

Our PERSIST-1 trial is a multicenter, open-label, randomized, controlled Phase 3 trial evaluating the efficacy and safety of pacritinib with that of best available therapy in patients with thrombocytopenia, or low platelets, and primary myelofibrosis, post-polycythemia vera myelofibrosis or post-essential thrombocythemia myelofibrosis. A total of 327 eligible patients were randomized 2:1 to receive either pacritinib 400 mg taken orally once daily or the best available therapy. Best available therapy includes any physician-selected treatment other than JAK2 inhibitors, and there is no exclusion by patient platelet count.

The primary endpoint for PERSIST-1 was the proportion of patients achieving a 35 percent or greater reduction in spleen volume from baseline to Week 24 as measured by MRI or CT, when compared with physician-specified best available therapy, excluding treatment with JAK2 inhibitors. The secondary endpoint was the percentage of patients achieving a 50 percent or greater reduction in Total Symptom Score, or TSS, from baseline to week 24 as measured by tracking specific symptoms on a form, or Patient Reported Outcome, or PRO, instrument. At the time of initiation of the trial, PERSIST-1 utilized the Myeloproliferative Neoplasm Symptom Assessment Form, or MPN-SAF TSS, the PRO instrument developed by Mayo Clinic, to measure TSS reduction. We collaborated with Mayo Clinic and the FDA and developed a modified instrument to be used as the endpoint for pacritinib clinical development. As a result, we amended the PERSIST-1 trial protocol to replace the original MPN-SAF TSS instrument with a new instrument, known as the MPN-SAF TSS 2.0, which is also being used for recording patient-reported outcomes for the PERSIST-2 trial. In connection with this amendment, we increased patient enrollment in the PERSIST-1 study from 270 to 327 patients. The trial enrolled patients at clinical sites in Europe, Australia, New Zealand, Russia and the U.S. The PRO Consortium, of which we are an active member, was formed by the non-profit Critical Path Institute in cooperation with the FDA and the medical products industry.

In March 2015, we reported positive top-line results for the primary endpoint from PERSIST-1. The trial met its primary endpoint in the intent-to-treat population with statistically significant activity observed in patients irrespective of their initial platelet count, including patients with very low platelet counts at study entry, a condition known as severe or life-threatening thrombocytopenia. The trial demonstrated that pacritinib treatment provided a statistically significant response rate ($p = 0.0003$) in spleen volume reduction in patients with myelofibrosis when compared to best available therapy, excluding treatment with JAK2 inhibitors, or BAT. Importantly, the trial results also demonstrated a significant difference among patients with platelet counts of less than 100,000 per microliter and less than 50,000 per microliter, both subgroups that were stratified at randomization. The magnitude of treatment effect was consistent with previously reported Phase 2 results, with the greatest reduction observed among the sickest patients (platelet counts $<50,000$ per microliter). Among 50 patients who were red blood cell transfusion dependent at study entry (≥ 6 units of RBC over 90 days pre entry), pacritinib therapy resulted in a clinically meaningful percentage of patients becoming transfusion independent compared to best available treatment. Seventy-nine percent (79%) of patients in the BAT arm of the study crossed over to pacritinib therapy.

The following table shows the proportion of patients randomized to pacritinib or BAT who achieved a $\geq 35\%$ reduction in spleen volume from baseline at Week 24 or up to Week 24 in the intent-to-treat, or ITT, population or evaluable patient population. The ITT population is the primary analysis, which included all randomized patients on pacritinib, $n=220$, or BAT, $n=107$. Patients without scans at baseline or at Week 24 are considered as non-responders for this primary analysis. In contrast, the evaluable patient population includes only patients with both baseline and Week 24 scans, $n=168$ for pacritinib and $n=85$ for BAT.

	Pacritinib	BAT	p-value
At Week 24 (Intent-to-Treat (1))	42/220 (19.1%)	5/107 (4.7%)	0.0003
Up to Week 24 (2) (Intent-to-Treat)	52/220 (23.6%)	5/107 (4.7%)	<0.0001
At Week 24 (Evaluable (3))	42/168 (25.0%)	5/85 (5.9%)	0.0001

- (1) Primary analysis included all patients randomized. Patients who missed baseline and Week 24 MRI or CT scans were counted as non-responders.
- (2) Includes patients who responded before week 24.
- (3) Analysis included patients who had assessment at both baseline and at Week 24.

The safety profile in the trial was consistent with prior Phase 2 trials. While the most common treatment emergent adverse events were diarrhea, nausea and vomiting, the incidence of grade 3 events was lower than observed in Phase 2 trials. No grade 4 gastrointestinal adverse events were reported. Three patients discontinued therapy and nine patients required dose reduction for diarrhea. Preliminary analysis suggests that very few patients discontinued treatment while on pacritinib or required a dose reduction due to treatment-related anemia or thrombocytopenia. Additional data from ongoing analyses along with top-line results from PERSIST-1 will be submitted for presentation at a scientific meeting.

Our ongoing PERSIST-2 trial is a multi-center, open-label, randomized, controlled Phase 3 trial evaluating pacritinib in up to 300 patients with myelofibrosis whose platelet counts are less than or equal to 100,000 per microlitre. This ongoing study is evaluating pacritinib as compared to best available therapy, including the approved JAK1/JAK2 inhibitor dosed according to the product label for myelofibrosis patients with thrombocytopenia. Patients are being randomized (1:1:1) to receive 200 mg pacritinib twice daily, 400 mg pacritinib once daily or best available therapy.

In October 2013, we reached an agreement with the FDA on a SPA for the PERSIST-2 trial regarding the planned design, endpoints and statistical analysis approach of the trial to be used in support of a potential regulatory submission. Under the SPA, the agreed upon co-primary endpoints are the percentage of patients achieving a 35 percent or greater reduction in spleen volume measured by MRI or CT scan from baseline to week 24 of treatment and the percentage of patients achieving a TSS reduction of 50 percent or greater using eight key symptoms as measured by the modified MPN-SAF TSS 2.0 diary from baseline to week 24. The trial is open for enrollment at clinical sites in the U.S., Canada, Europe, Australia, New Zealand and Russia. Additional study details are available at www.PERSISTprogram.com or www.clinicaltrials.gov, study identifier NCT02055781; however, the information found on such website is not incorporated by reference into this Annual Report on Form 10-K.

Development in Other Indications

In January 2014, we announced that an international cooperative group Phase 2 clinical trial of pacritinib in adult patients with relapsed AML with mutations of the FLT3 gene. Mutation of the FLT3 gene is found in approximately one-third of AML patients and is an independent risk factor for poor prognosis. Pacritinib has demonstrated encouraging activity in preclinical models of AML with mutated FLT3 gene, including additional FLT3 mutations that confer resistance to other targeted FLT3 agents. The trial is being conducted by the AML Working Group of the National Cancer Research Institute Haematological Oncology Study Group in AML and high risk MDS under the sponsorship of Cardiff University and supported by Cancer Research UK.

Contractual Arrangements Relating to Pacritinib

For a discussion of our milestone and royalty payment potential and other contractual terms under the Baxter Agreement, together with a discussion of the agreement under which we originally acquired pacritinib (and under which we have certain royalty and milestone payment obligations), see Part I, Item 1, “Business—License Agreements and Additional Milestone Activities”.

Tosedostat

Tosedostat is a first-in-class selective inhibitor of aminopeptidases, which are required by tumor cells to provide amino acids necessary for growth and tumor cell survival. Tosedostat has demonstrated anti-tumor responses in blood-related cancers and solid tumors in Phase 1 and 2 clinical studies. Several ongoing Phase 2 cooperative group sponsored trials and ISTs are evaluating the activity of tosedostat in combination with standard agents in patients with AML or MDS. We anticipate that data from these signal-finding trials may inform the appropriate design for a Phase 3 study to support potential regulatory approval. In June 2014, we announced the initiation of an international cooperative group Phase 2/3 clinical trial of tosedostat in combination with low-dose cytarabine in older patients with AML or high risk MDS. The study is being conducted by the National Cancer Research Institute Haematological Oncology Study Group under the sponsorship of Cardiff University. In this Phase 2/3 study, referred to as AML Less Intensive (LI-1), patients are being randomized to standard treatment, low dose cytarabine, versus one of five novel investigational treatments, one of which is tosedostat, each in combination with low dose cytarabine. The trial will utilize a “Pick a Winner” trial design. Overall survival will serve as the primary endpoint of this trial.

In December 2014, results from an investigator-initiated Phase 2 clinical trial of tosedostat in combination with cytarabine or decitabine in newly diagnosed older patients with AML or high-risk MDS were presented at the American Society of Hematology Annual Meeting. The Phase 2 trial was designed to test the efficacy of tosedostat in combination with low intensity therapy for older patients with previously untreated AML or high-risk MDS not considered candidates for standard intensive therapy. This presentation reported on the results of 34 patients (median age was 70) that were enrolled. Patients were randomized for treatment with tosedostat in combination with either cytarabine or decitabine. Eighteen out of 34 (41 percent) patients in this cohort had either a complete response (CR; n=14, 41 percent) or complete response with incomplete blood count recovery (CRi; n=4, 12 percent). The percentage of complete responses was comparable between arms. The study achieved its primary objective with 27 (79 percent)

patients alive at four months. Median overall survival was encouraging at approximately 16.7 months for both study arms. Tosedostat combination therapy was well tolerated and predominantly administered as an outpatient therapy. The primary side effects of the combination therapy, the majority of which were associated with the cytarabine arm, included febrile neutropenia (47 percent), pulmonary infections (32 percent) and sepsis (21 percent). Clinically significant non-hematological toxicities were uncommon and predominantly low grade.

We have an exclusive worldwide license agreement for tosedostat, as discussed in more detail in Part I, Item 1, “Business—License Agreements and Additional Milestone Activities—Chroma”

Opaxio

Opaxio is a novel biologically-enhanced chemotherapeutic agent that links paclitaxel to a biodegradable polyglutamate polymer, resulting in a new chemical entity. Taxanes, including paclitaxel (Taxol®) and docetaxel (Taxotere®), are widely used for the treatment of various solid tumors, including non-small cell lung, ovarian, breast and prostate cancers.

Opaxio was designed to deliver paclitaxel preferentially to tumor tissue. By linking paclitaxel to a biodegradable amino acid carrier, the conjugated chemotherapeutic agent is inactive in the bloodstream, sparing normal tissues the toxic side effects of chemotherapy. Once inside tumor tissue, the conjugated chemotherapeutic agent is activated and released by the action of an enzyme called cathepsin B. Opaxio remains stable in the bloodstream for several days after administration; this prolonged circulation allows the passive accumulation of the drug in tumor tissue.

The development of Opaxio as a potential maintenance therapy for women with advanced stage ovarian cancer who achieve a complete remission following first-line therapy with paclitaxel and carboplatin is being conducted and managed by the Gynecologic Oncology Group, or GOG, now part of NRG Oncology, which is one of the National Cancer Institute's funded cooperative cancer research groups focused on the study of gynecologic malignancies.

The GOG-0212 study is a randomized, multicenter, open-label Phase 3 trial of either monthly Opaxio or paclitaxel for up to 12 consecutive months compared to surveillance among women with advanced ovarian cancer who have no evidence of disease following first-line platinum-taxane based therapy. For purposes of registration, the primary endpoint of the study is overall survival of Opaxio compared to no maintenance therapy. Secondary endpoints are PFS, safety and quality of life. The statistical analysis plan calls for up to four interim analyses and one final analysis, each with boundaries for early closure for superior efficacy or for futility. Additional information about GOG-0212 may be found at www.clinicaltrials.gov, study identifier NCT00108745; however, the information found on such website is not incorporated by reference into this Annual Report on Form 10-K.

We acquired an exclusive worldwide license for rights to paclitaxel poligumex and certain polymer technology from PG-TXL Company, L.P., or PG-TXL, in November 1998 as discussed below in Part I, Item 1, "Business—License Agreements and Additional Milestone Activities—PG-TXL".

Research and Development Expenses

Research and development is essential to our business. We spent \$64.6 million, \$33.6 million and \$33.2 million in 2014, 2013 and 2012, respectively, on company-sponsored research and development activities. The development of a product candidate involves inherent risks and uncertainties, including, among other things, that we cannot predict with any certainty the pace of enrollment of our clinical trials. As a result, we are unable to provide the nature, timing and estimated costs of the efforts necessary to complete the development of pacritinib, tosedostat and Opaxio or to complete the post-approval commitment study of PIXUVRI. Further, third parties are conducting clinical trials for tosedostat and Opaxio. Even after a clinical trial is enrolled, preclinical and clinical data can be interpreted in different ways, which could delay, limit or preclude regulatory approval and advancement of this compound through the development process. For these reasons, among others, we cannot estimate the date on which clinical development of these product candidates will be completed or when, if ever, we will generate material net cash inflows from PIXUVRI or be able to commence commercialization of pacritinib, tosedostat and Opaxio. For additional information relating to our research and development expenses and associated risks, see Part II, Item 7, "Management's Discussion and Analysis of Financial Condition and Results of Operations—Results of Operations—Years Ended December 31, 2014 and 2013—Operating costs and expenses—Research and development expenses" and Part I, Item 1A, "Risk Factors".

License Agreements and Additional Milestone Activities

Servier

In September 2014, we entered into the Servier Agreement pursuant to which we granted Servier an exclusive and sublicensable (subject to certain conditions) royalty-bearing license with respect to the development and commercialization of PIXUVRI for use in pharmaceutical products outside of the CTI Territory (defined below). We retained rights to PIXUVRI in Austria, Denmark, Finland, Germany, Israel, Norway, Sweden, Turkey, the U.K. and the U.S., or collectively, the CTI Territory.

We received an upfront payment in October 2014 of €14.0 million (or \$17.8 million using the currency exchange rate as of the date we received the funds in October 2014). In addition, subject to the achievement of certain conditions, we are eligible to receive milestone payments under the Servier Agreement in the aggregate amount of up to €89.0 million, which is comprised of the following: up to €49.0 million in potential clinical and regulatory milestone payments (of which €9.5 million is payable upon occurrence of certain enrollment events in connection with the PIX306 study for PIXUVRI); and up to €40.0 million in potential sales-based milestone payments. Of the foregoing potential milestone payments, we received a €1.5 million milestone payment in February 2015 relating to the attainment of reimbursement approval for PIXUVRI in Spain. In addition, for a number of years following the first commercial sale of a product containing PIXUVRI in the respective country, regardless of patent expiration or expiration of regulatory exclusivity rights, we are eligible to receive tiered royalty payments ranging from a low-double digit percentage up to a percentage in the mid-twenties based on net sales of PIXUVRI products, subject to certain reductions of up to mid-double digit percentages under certain circumstances.

Unless otherwise agreed by the parties, (i) certain development costs incurred pursuant to a development plan and (ii) certain marketing costs incurred pursuant to a marketing plan will be shared equally by the parties, subject to a maximum dollar obligation of each party.

The Servier Agreement will expire on a country-by-country basis upon the expiration of the royalty terms in the countries outside of the CTI Territory, at which time all licenses granted to Servier would become perpetual and royalty-free. Each party may terminate the Servier Agreement in the event of an uncured repudiatory breach (as defined under English law) of the other party's obligations. Servier may terminate the Servier Agreement without cause on a country-by-country basis upon written notice to us within a specified time period or upon written notice within a certain period of days in the event of (i) certain safety or public health issues involving PIXUVRI or (ii) cessation of certain marketing authorizations. In the event of a termination prior to the expiration date, rights granted to Servier will terminate, subject to certain exceptions.

Baxter

In November 2013, we entered into the Baxter Agreement for the development and commercialization of pacritinib for use in oncology and potentially additional therapeutic areas. Under the Baxter Agreement, we granted Baxter an exclusive, worldwide (subject to co-promotion rights discussed below), royalty-bearing, non-transferable license (which is sub-licensable under certain circumstances) relating to pacritinib. Licensed products under the Baxter Agreement consist of products in which pacritinib is an ingredient.

Baxter paid us an upfront payment of \$60 million, which included a \$30 million investment in our equity. The Baxter Agreement also provides for us to receive potential additional payments of up to \$302 million upon the successful achievement of certain development and commercialization milestones, comprised of \$112 million of potential clinical, regulatory and commercial launch milestone payments, and potential additional sales milestone payments of up to \$190 million. Of such potential milestones payments, we have received \$20 million to date relating to the achievement of a clinical milestone. We and Baxter will jointly commercialize and share any profits and losses on sales of pacritinib in the U.S.

We were responsible for all development costs incurred prior to January 1, 2014, and are responsible for approximately \$96 million in U.S. and E.U. development costs incurred thereafter, subject to potential adjustment in certain circumstances. All development costs exceeding the \$96 million threshold will generally be shared as follows: (i) costs generally applicable worldwide will be shared 75 percent to Baxter and 25 percent to us, (ii) costs applicable to territories exclusive to Baxter will be 100 percent borne by Baxter and (iii) costs applicable exclusively to co-promotion in the U.S. will be shared equally between the parties, subject to certain exceptions.

Outside the U.S., we are eligible to receive tiered high single-digit to mid-teen percentage royalty payments based on net sales for myelofibrosis, and higher double digit royalties for other indications, subject to reduction by up to 50 percent if (i) Baxter is required to obtain third party royalty-bearing licenses to fulfill its obligations under the Baxter Agreement and (ii) in any jurisdiction where there is no longer either regulatory exclusivity or patent protection.

The Baxter Agreement will expire when Baxter has no further obligation to pay royalties to us in any jurisdiction, at which time the licenses granted to Baxter will become perpetual and royalty-free. We or Baxter may terminate the Baxter Agreement prior to its expiration in certain circumstances. Following the one-year anniversary of receipt of regulatory approval in certain countries, we may terminate the Baxter Agreement as to one or more such countries if Baxter has not undertaken requisite regulatory or commercialization efforts in the applicable country and certain other conditions are met. Baxter may terminate the Baxter Agreement earlier than its expiration in certain circumstances including (i) in the event development costs for myelofibrosis for the period commencing January 1, 2014 are reasonably projected to exceed a specified threshold, (ii) as to some or all countries in the event of commercial failure of the licensed product or (iii) without cause following the one-year anniversary of the effective date of the Baxter Agreement, provided that such termination will have a lead-in period of six months before it becomes effective.

Additionally, either party may terminate the Baxter Agreement prior to its expiration in events of force majeure, or the other party's uncured material breach or insolvency. In the event of a termination prior to the expiration date, rights in pacritinib will revert to us.

University of Vermont

We entered into an agreement with the University of Vermont, or UVM, in March 1995, as amended, or the UVM Agreement, which grants us an exclusive sublicensable license for the rights to PIXUVRI. Pursuant to the UVM Agreement, we acquired the rights to make, have made, sell and use PIXUVRI, and we are obligated to make royalty payments to UVM ranging from low single digits to mid-single digits as a percentage of net sales. The higher royalty rate is payable for net sales in countries where specified UVM licensed patents exist, or where we have obtained orphan drug protection, until such UVM patents or such protection no longer exists. For a period of ten years after first commercialization of PIXUVRI, the lower royalty rate is payable for net sales in such countries after expiration of the designated UVM patents or loss of orphan drug protection, and in all other countries without such specified UVM patents or orphan drug protection. Unless otherwise terminated, the term of the UVM Agreement continues for the life of the licensed patents in those countries in which a licensed patent exists, and continues for ten years after the first sale of PIXUVRI in those countries where no such patents exist. We may terminate the UVM Agreement, on a country-by-country basis or on a patent-by-patent basis, at any time upon advance written notice. UVM may terminate the UVM Agreement upon advance written notice in the event royalty payments are not made. In addition, either party may terminate the UVM Agreement in the event of an uncured material breach of the UVM Agreement by the other party or in the event of bankruptcy of the other party.

S*BIO

We acquired the compounds SB1518 (which is referred to as “pacritinib”) and SB1578, which inhibit JAK2 and FLT3, from S*BIO Pte Ltd., or S*BIO, in May 2012. Under our agreement with S*BIO, we are required to make milestone payments to S*BIO up to an aggregate amount of \$132.5 million if certain U.S., E.U. and Japanese regulatory approvals are obtained or if certain worldwide net sales thresholds are met in connection with any pharmaceutical product containing or comprising any compound that we acquired from S*BIO for use for specific diseases, infections or other conditions. At our election, we may pay up to 50 percent of any milestone payments to S*BIO through the issuance of shares of our common stock or shares of our preferred stock convertible into our common stock. In addition, S*BIO will also be entitled to receive royalty payments from us at incremental rates in the low single-digits based on certain worldwide net sales thresholds on a product-by-product and country-by-country basis.

Chroma

In October 2014, we entered into an asset purchase agreement, or the Chroma APA, with Chroma Therapeutics Limited, or Chroma, pursuant to which we acquired all of Chroma’s right, title and interest in the compound tosedostat and certain related assets. Concurrently, we and Chroma terminated our Co-Development and License Agreement relating to tosedostat, or the Chroma License Agreement, previously entered into on March 11, 2011, thereby eliminating potential future milestone payments thereunder of up to \$209.0 million, and we acquired an exclusive worldwide license with respect to tosedostat directly from Vernalis R&D Limited, or Vernalis.

As consideration under the Chroma APA, we issued an aggregate of 9,000 shares of the Company’s Series 20 convertible preferred stock, of which 7,920 have been delivered to Chroma. The remaining 1,080 shares are being held in escrow for nine months and will be applied towards any indemnification obligations of Chroma as set forth in the Chroma APA.

Vernalis

Concurrently with the termination of the Chroma License Agreement and the execution of the Chroma APA, we also entered into an amended and restated exclusive license agreement with Vernalis, or the Vernalis License Agreement, for the exclusive worldwide right to use certain patents and other intellectual property rights to develop, market and commercialize tosedostat and certain other compounds, as well as a deed of novation pursuant to which all rights of Chroma under its prior license agreement with Vernalis relating to tosedostat were novated to us. Under the Vernalis

License Agreement, we have agreed to make tiered royalty payments of no more than a high single digit percentage of net sales of products containing licensed compounds, with such obligation to continue on a country-by-country basis for the longer of ten years following commercial launch or the expiry of relevant patent claims.

The Vernalis License Agreement will terminate when the royalty obligations expire, although the parties have early termination rights under certain circumstances, including the following: (i) we have the right to terminate, with three months' notice, upon the belief that the continued development of tosedostat or any of the other licensed compounds is not commercially viable; (ii) Vernalis has the right to terminate in the event of our uncured failure to pay sums due; and (iii) either party has the right to terminate in event of the other party's uncured material breach or insolvency.

Gynecologic Oncology Group (GOG)

We entered into an agreement with the GOG, now part of NRG Oncology, in March 2004, as amended, related to the GOG-0212 trial of Opaxio it is conducting in patients with ovarian cancer. Pursuant to the terms of such agreement, we paid an aggregate of \$1.2 million in milestone payments during 2014 based on certain enrollment milestones achieved. We may be required to pay up to an additional \$1.0 million upon the attainment of certain other milestones, of which \$0.5 million has been recorded in accrued expenses as of December 31, 2014.

PG-TXL

In November 1998, we entered into an agreement, or the PG-TXL Agreement, as amended, with PG-TXL Company, L.P., or PG-TXL, which grants us an exclusive worldwide license for the rights to Opaxio and to all potential uses of PG-TXL's polymer technology. Pursuant to the PG-TXL Agreement, we acquired the rights to research, develop, manufacture, market and sell anti-cancer drugs developed using this polymer technology. We are obligated to make payments to PG-TXL upon the achievement of certain development and regulatory milestones of up to \$14.4 million. The timing of the remaining milestone payments under the PG-TXL Agreement is based on trial commencements and completions of compounds protected by PG-TXL license rights, and regulatory and marketing approval of those compounds by the FDA and the EMA. Additionally, we are required to make royalty payments to PG-TXL based on net sales. Our royalty obligations range from low to mid single-digits as a percentage of net sales. Unless otherwise terminated, the term of the PG-TXL Agreement continues until no royalties are payable to PG-TXL. We may terminate the PG-TXL Agreement upon advance written notice to PG-TXL in the event of issues regarding the safety of the products licensed pursuant to the PG-TXL Agreement during development or clinical data obtained reveal a materially adverse tolerability profile for the licensed product in humans, or for any reason upon advance written notice. In addition, either party may terminate the PG-TXL Agreement upon advance written notice in the event certain license fee payments are not made; in the event of an uncured material breach of the respective material obligations and conditions of the PG-TXL Agreement; or in the event of liquidation or bankruptcy of the other party.

Novartis

In January 2014, we entered into a termination agreement, or the Novartis Termination Agreement, with Novartis International Pharmaceutical Ltd., or Novartis, to reacquire the rights to PIXUVRI and Opaxio, or collectively, the Compounds, previously granted to Novartis under our agreement with Novartis entered into in September 2006, as amended, or the Original Agreement. Pursuant to the Novartis Termination Agreement, the Original Agreement was terminated in its entirety, except for certain customary provisions, including those pertaining to confidentiality and indemnification, which survive termination.

Under the Novartis Termination Agreement, we agreed not to transfer, license, sublicense or otherwise grant rights with respect to intellectual property of the Compounds unless the recipient thereof agrees to be bound by the terms of the Novartis Termination Agreement. We also agreed to provide potential payments to Novartis, including a percentage ranging from the low double-digits to the mid-teens, of any consideration received by us or our affiliates in connection with any transfer, license, sublicense or other grant of rights with respect to intellectual property of PIXUVRI or Opaxio, respectively; provided that such payments will not exceed certain prescribed ceilings in the low single-digit millions. As a result of having received the upfront payment under the Servier Agreement, we were obligated to pay Novartis €2.1 million (or \$2.7 million using the currency exchange rate as of the date of payment in October 2014). Novartis is entitled to receive potential payments of up to \$16.6 million upon the successful achievement of certain sales milestones of the Compounds. We are also obligated to pay Novartis tiered low single-digit percentage royalty payments for the first several hundred million in annual net sales, and ten percent royalty payments thereafter based on annual net sales of each Compound, subject to reduction in the event generic drugs are introduced and sold by a third party, causing the sale of PIXUVRI or Opaxio to fall by a percentage in the high double-digits. To the extent we are required to pay royalties on net sales of Opaxio pursuant to the PG-TXL Agreement, we may credit a percentage of the amount of such royalties paid to those payable to Novartis, subject to

certain exceptions. Royalty payments for both PIXUVRI and Opaxio are subject to certain minimum floor percentages in the low single-digits.

Nerviano Medical Sciences

Our license agreement dated October 6, 2006 with Nerviano Medical Sciences, S.r.l. for brostallicin, a synthetic DNA minor groove binding agent that has demonstrated anti-tumor activity, provides for the potential payment by us of up to \$80 million in milestone payments based on the achievement of certain product development results.

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Teva Pharmaceutical Industries Ltd.

In June 2005, we entered into an acquisition agreement with Cephalon, Inc., or Cephalon, pursuant to which we divested of the compound, TRISENOX. Cephalon was subsequently acquired by Teva Pharmaceutical Industries Ltd., or Teva. Under this agreement, we have the right to receive up to \$100 million in payments upon achievement by Teva of specified sales and development milestones related to TRISENOX. To date, we have received \$20.0 million of such potential milestone payments as a result of having achieved certain sales milestones.

Patents and Proprietary Rights

We dedicate significant resources to protecting our intellectual property, which is important to our business. We have filed numerous patent applications in the U.S. and various other countries seeking protection of inventions originating from our research and development, and we have also obtained rights to various patents and patent applications under licenses with third parties and through acquisitions. Patents have been issued on many of these applications. We have pending patent applications or issued patents in the U.S. and foreign countries directed to PIXUVRI, pacritinib, tosedostat, Opaxio and other product candidates. However, the lives of these patents are limited. Patents for the individual products extend for varying periods according to the date of the patent filing or grant and the legal term of patents in the various countries where patent protection is obtained. The Opaxio-directed patents will expire on various dates ranging from 2017 through 2018. The pacritinib-directed patents will expire from 2026 through 2029. The PIXUVRI-directed U.S. patents expired in 2014. While we have a pending PIXUVRI-directed U.S. patent application (which, if granted, would expire in 2023), we have to date been unable to obtain issuance of a patent for such application (and no assurances can be made that we will ever receive such patent). The tosedostat-directed patents will expire from 2017 to 2018.

The PIXUVRI-directed patents currently in force in Europe will begin to expire in late March 2015 through a portion of 2023. Some of these European patents are subject to Supplementary Protection Certificates such that the extended patents will expire from 2020 to 2027. Although we are seeking to obtain Supplementary Protection Certificates for certain other of our PIXUVRI-directed patents in Europe that could provide extensions through 2027 in some additional countries in Europe, there can be no guarantee of extensions of PIXUVRI-directed or other patents in other countries. The risks and uncertainties associated with our intellectual property, including our patents, are discussed in more detail in Part I, Item 1A, "Risk Factors".

Manufacturing, Distribution and Associated Operations

Our manufacturing strategy utilizes third party contractors for the procurement and manufacture, as applicable, of raw materials, active pharmaceutical ingredients and finished drug product, as well as for labeling, packaging, storage and distribution of our compounds and associated supply chain operations. As our business continues to expand, we expect that our manufacturing, distribution and related operational requirements will increase correspondingly. One item of increasing importance relates to our commercial supply needs; while we currently have a commercial supply arrangement for PIXUVRI, we do not presently have any such arrangement in place for pacritinib (or for our other product candidates). In particular, procuring a qualified commercial supplier for pacritinib has become an important objective as we continue to advance the development of pacritinib and position such product for potential commercialization.

Integral to our manufacturing strategy is our quality control and quality assurance program, which includes standard operating procedures and specifications with the goal that our compounds are manufactured in accordance with current Good Manufacturing Practices, or cGMPs, and other applicable global regulations. The cGMP compliance includes strict adherence to regulations for quality control, quality assurance and the maintenance of records and documentation. Manufacturing facilities for products and product candidates must meet cGMP requirements, and commercialized products must have acquired FDA, EMA and any other applicable regulatory approval. In this regard, we expect to continue to rely on contract manufacturers to produce sufficient quantities of our compounds in

accordance with cGMPs for use in clinical trials and distribution.

We believe our operational strategy of utilizing qualified outside vendors in the foregoing manner allows us to direct our financial and managerial resources to development and commercialization activities, rather than to the establishment and maintenance of a manufacturing and distribution infrastructure.

Competition

Competition in the pharmaceutical and biotechnology industries is intense. We face competition from a variety of companies focused on developing oncology drugs. We compete with large pharmaceutical companies and with other specialized biotechnology companies. In addition to the specific competitive factors discussed below, new anti-cancer drugs that may be developed and marketed in the future could compete with our various compounds.

With respect to PIXUVRI, while there are no other products approved in the E.U. as monotherapy for the treatment of adult patients with multiply relapsed or refractory aggressive NHL, there are other agents approved to treat aggressive NHL that could be used in this setting, including both branded and generic anthracyclines as well as mitoxantrone.

With respect to our other investigational candidates, if approved, they may face competition from compounds that are currently approved or may be approved in the future. Pacritinib would compete with Incyte, which markets Jakafi® in the U.S., and potentially other candidates in development that target JAK inhibition to treat cancer. Tosedostat would compete with currently marketed products such as Dacogen®, Vidaza®, Revlimid®, Thalomid® and Clolar®. Opaxio would compete with other taxanes, epothilones, and other cytotoxic agents, which inhibit cancer cells by a mechanism similar to taxanes, or similar products such as paclitaxel and generic forms of paclitaxel, docetaxel, Tarceva®, Avastin®, Alimta®, and Abraxane®.

Many of our existing or potential competitors have substantially greater financial, technical and human resources than us and may be better equipped to develop, manufacture and market products. Smaller companies may also prove to be significant competitors, particularly through collaborative arrangements with large pharmaceutical and established biotechnology companies. Many of these competitors have products that have been approved or are in development and operate large, well-funded research and development programs.

Companies that complete clinical trials, obtain required regulatory approvals and commence commercial sales of their products before us may achieve a significant competitive advantage if their products work through a similar mechanism as our products and if the approved indications are similar. A number of biotechnology and pharmaceutical companies are developing new products for the treatment of the same diseases being targeted by us. In some instances, such products have already entered late-stage clinical trials or received FDA or European Commission approval. However, cancer drugs with distinctly different mechanisms of action are often used together in combination for treating cancer, allowing several different products to target the same cancer indication or disease type. Such combination therapy is typically supported by clinical trials that demonstrate the advantage of combination therapy over that of a single-agent treatment.

We believe that our ability to compete successfully will be based on our ability to create and maintain scientifically advanced technology, develop proprietary products, attract and retain scientific personnel, obtain patent or other protection for our products, obtain required regulatory approvals and manufacture and successfully market our products, either alone or through outside parties. We will continue to seek licenses with respect to technology related to our field of interest and may face competition with respect to such efforts. See the risk factor, “We face direct and intense competition from our competitors in the biotechnology and pharmaceutical industries, and we may not compete successfully against them.” in Part I, Item 1A, “Risk Factors” of this Annual Report on Form 10-K for additional information regarding the risks and uncertainties we face due to competition in our industry.

Government Regulation

We are subject to extensive regulation by the FDA and other federal, state, and local regulatory agencies. The Federal Food, Drug, and Cosmetic Act, or the FDCA, and its implementing regulations set forth, among other things, requirements for the testing, development, manufacture, quality control, safety, effectiveness, approval, labeling, storage, record keeping, reporting, distribution, import, export, advertising and promotion of our products. Our activities in other countries will be subject to regulation that is similar in nature and scope as that imposed in the U.S., although there can be important differences. Additionally, some significant aspects of regulation in the E.U. are addressed in a centralized way through the EMA and the European Commission, but country-specific regulation by the competent authorities of the E.U. member states remains essential in many respects.

U.S. Regulation

In the U.S., the FDA regulates drugs under the FDCA and its implementing regulations, through review and approval of New Drug Applications, or NDAs. NDAs require extensive studies and submission of a large amount of data by the applicant.

Drug Development

Preclinical Testing. Before testing any compound in human subjects in the U.S., a company must generate extensive preclinical data. Preclinical testing generally includes laboratory evaluation of product chemistry and formulation, as well as toxicological and pharmacological studies in several animal species to assess the quality and safety of the product. Animal studies must be performed in compliance with the FDA's Good Laboratory Practice regulations and the U.S. Department of Agriculture's Animal Welfare Act.

IND Application. Human clinical trials in the U.S. cannot commence until an investigational new drug, or IND, application is submitted and becomes effective. A company must submit preclinical testing results to the FDA as part of the IND application, and the FDA must evaluate whether there is an adequate basis for testing the drug in initial clinical studies in human volunteers. Unless the FDA raises concerns, the IND application becomes effective 30 days following its receipt by the FDA. Once human clinical trials have commenced, the FDA may stop the clinical trials by placing them on “clinical hold” because of concerns about the safety of the product being tested, or for other reasons.

Clinical Trials. Clinical trials involve the administration of the drug to healthy human volunteers or to patients, under the supervision of a qualified investigator. The conduct of clinical trials is subject to extensive regulation, including compliance with the FDA’s bioresearch monitoring regulations and Good Clinical Practice, or GCP, requirements, which establish standards for conducting, recording data from and reporting the results of, clinical trials, and are intended to assure that the data and reported results are credible and accurate, and that the rights, safety, and well-being of study participants are protected. Clinical trials must be conducted under protocols that detail the study objectives, parameters for monitoring safety, and the efficacy criteria, if any, to be evaluated. Each protocol is reviewed by the FDA as part of the IND application. In addition, each clinical trial must be reviewed, approved, and conducted under the auspices of an institutional review board, or IRB, at the institution conducting the clinical trial. Companies sponsoring the clinical trials, investigators, and IRBs also must comply with regulations and guidelines for obtaining informed consent from the study subjects, complying with the protocol and investigational plan, adequately monitoring the clinical trial and timely reporting adverse events. Foreign studies conducted under an IND application must meet the same requirements that apply to studies being conducted in the U.S. Data from a foreign study not conducted under an IND application may be submitted in support of an NDA if the study was conducted in accordance with GCP and the FDA is able to validate the data.

A study sponsor is required to submit certain details about active clinical trials and clinical trial results to the National Institutes of Health for public posting on <http://clinicaltrials.gov>. Human clinical trials typically are conducted in three sequential phases, although the phases may overlap with one another:

- Phase 1 clinical trials include the initial administration of the investigational drug to humans, typically to a small group of healthy human subjects, but occasionally to a group of patients with the targeted disease or disorder. Phase 1 clinical trials generally are intended to determine the metabolism and pharmacologic actions of the drug, the side effects associated with increasing doses, and, if possible, to gain early evidence of effectiveness.
- Phase 2 clinical trials generally are controlled studies that involve a relatively small sample of the intended patient population, and are designed to develop data regarding the product’s effectiveness, to determine dose response and the optimal dose range and to gather additional information relating to safety and potential adverse effects.
- Phase 3 clinical trials are conducted after preliminary evidence of effectiveness has been obtained, and are intended to gather the additional information about safety and effectiveness necessary to evaluate the drug’s overall risk-benefit profile, and to provide a basis for physician labeling. Generally, Phase 3 clinical development programs consist of expanded, large-scale studies of patients with the target disease or disorder to obtain statistical evidence of the efficacy and safety of the drug, or the safety, purity, and potency of a biological product, at the proposed dosing regimen.

The sponsoring company, the FDA or the IRB may suspend or terminate a clinical trial at any time on various grounds, including a finding that the subjects are being exposed to an unacceptable health risk. Further, success in early-stage clinical trials does not assure success in later-stage clinical trials. Data obtained from clinical activities are not always conclusive and may be subject to alternative interpretations that could delay, limit or prevent regulatory approval.

The FDA and IND application sponsor may agree in writing on the design and size of clinical trials intended to form the primary basis of an effectiveness claim in an NDA application. This process is known as a SPA. These agreements may not be changed after the clinical trials begin, except in limited circumstances. The existence of a SPA, however, does not assure approval of a product candidate.

Drug Approval

Assuming successful completion of the required clinical testing, the results of the preclinical studies and of the clinical trials, together with other detailed information, including information on the manufacture and composition of the investigational product, are submitted to the FDA in the form of an NDA requesting approval to market the product for one or more indications. The testing and approval process requires substantial time, effort and financial resources. Submission of an NDA requires payment of a substantial review user fee to the FDA. The FDA will review the application and may deem it to be inadequate to support commercial marketing, and there can be no assurance that any product approval will be granted on a timely basis, if at all. The FDA may also seek the advice of an advisory committee, typically a panel of clinicians practicing in the field for which the product is intended, 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 FDA has various programs, including breakthrough therapy, fast track, priority review and accelerated approval that are intended to expedite or simplify the process for reviewing drugs and/or provide for approval on the basis of surrogate endpoints. 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. We cannot be sure that any of our drugs will qualify for any of these programs, or that, if a drug does qualify, the review time will be reduced or the product will be approved.

Before approving a NDA, the FDA usually will inspect the facility or the facilities where the product is manufactured, tested and distributed and will not approve the product unless cGMP compliance is satisfactory. If the FDA evaluates the NDA and the manufacturing facilities as acceptable, the FDA may issue an approval letter, or in some cases, a complete response letter. A complete response letter contains a number of conditions that must be met in order to secure final approval of the NDA. When and if those conditions have been met to the FDA's satisfaction, the FDA will issue an approval letter. The approval letter authorizes commercial marketing of the drug for specific indications. As a condition of approval, the FDA may require post-marketing testing and surveillance to monitor the product's safety or efficacy, or impose other post-approval commitment conditions.

In some circumstances, post-marketing testing may include post-approval clinical trials, sometimes referred to as Phase 4 clinical trials, which are used primarily to gain additional experience from the treatment of patients in the intended population, particularly for long-term safety follow-up. In addition, the FDA may require a Risk Evaluation and Mitigation Strategy, or REMS, to ensure that the benefits outweigh the risks. A REMS can include medication guides, physician communication plans and elements to assure safe use, such as restricted distribution methods, patient registries or other risk mitigation tools.

After approval, certain changes to the approved product, such as adding new indications, making certain manufacturing changes or making certain additional labeling claims, are subject to further FDA review and approval. Obtaining approval for a new indication generally requires that additional clinical trials be conducted.

Post-Approval Requirements

Holders of an approved NDA are required to: (i) report certain adverse reactions to the FDA; (ii) comply with certain requirements concerning advertising and promotional labeling for their products; and (iii) continue to have quality control and manufacturing procedures conform to cGMP after approval. The FDA periodically inspects the sponsor's records related to safety reporting and/or manufacturing and distribution facilities; this latter effort includes assessment of compliance with cGMP. Accordingly, manufacturers must continue to expend time, money and effort in the area of production, quality control and distribution to maintain cGMP compliance. Future FDA inspections may identify compliance issues at manufacturing facilities that may disrupt production or distribution, or require substantial resources to correct. In addition, discovery of problems with a product after approval may result in restrictions on a product, manufacturer or holder of an approved NDA, including withdrawal of the product from the market.

Marketing of prescription drugs is also subject to significant regulation through federal and state agencies tasked with consumer protection and prevention of medical fraud, waste and abuse. After approval in the U.S., we must comply with FDA's regulation of drug promotion and advertising, including restrictions on off-label promotion, and we comply with federal anti-kickback statutes, limitations on gifts and payments to physicians and reporting of payments to certain third-parties, among other requirements. In December 2007, we entered into a corporate integrity agreement with the Office of the Inspector General, Health and Human Services as part of our settlement agreement with the U.S. Attorney's Office for the Western District of Washington arising out of their investigation into certain of our prior marketing practices relating to TRISENOX, which was divested to Cephalon in July 2005. The term of the corporate integrity agreement, and the requirement that we establish a compliance committee and compliance program and

adopt a formal code of conduct, expired as of December 22, 2012. However, we intend to continue to abide by the Pharmaceutical Research and Manufacturers of America Code and FDA regulations.

Failure to comply with applicable U.S. requirements may subject us to administrative or judicial sanctions, such as clinical holds, FDA refusal to approve pending NDAs or supplemental applications, warning letters, product recalls, product seizures, total or partial suspension of production or distribution, injunctions and/or criminal prosecution.

Non-U.S. Regulation

Before our products can be marketed outside of the U.S., they are subject to regulatory approval similar to that required in the U.S., although the requirements governing the conduct of clinical trials, including additional clinical trials that may be required, product licensing, pricing and reimbursement vary widely from country to country. No action can be taken to market any product in a country until an appropriate application has been approved by the regulatory authorities in that country. The current approval process varies from country to country, and the time spent in gaining approval varies from that required for FDA approval. In certain countries, the sales price of a product must also be approved. The pricing review period often begins after market approval is granted. Even if a product is approved by a regulatory authority, satisfactory prices may not be approved for such product.

In the E.U., marketing authorizations for medicinal products can be obtained through several different procedures founded on the same basic regulatory process. The centralized procedure is mandatory for certain medicinal products, including orphan medicinal products, medicinal products derived from certain biotechnological processes, advanced therapy medicinal products and certain other new medicinal products containing a new active substance for the treatment of certain diseases. It is optional for certain other products, including medicinal products that are significant therapeutic, scientific or technical innovations, or whose authorization would be in the interest of public or animal health. The centralized procedure allows a company to submit a single application to the EMA which will provide a positive opinion regarding the application if it meets certain quality, safety, and efficacy requirements. Based on the opinion of the EMA, the European Commission takes a final decision to grant a centralized marketing authorization which is valid in all 28 E.U. Member States and three of the four European Free Trade Association states (Iceland, Liechtenstein and Norway).

Unlike the centralized authorization procedure, the decentralized marketing authorization procedure requires a separate application to, and leads to separate approval by, the competent authorities of each E.U. Member State in which the product is to be marketed. One national competent authority selected by the applicant, the Reference Member State, assesses the application for marketing authorization. Following a positive opinion by the competent authority of the Reference Member State the competent authorities of the other E.U. Member States, Concerned Member States are subsequently required to grant marketing authorization for their territory on the basis of this assessment except where grounds of potential serious risk to public health require this authorization to be refused. The mutual recognition procedure is similarly based on the acceptance by the competent authorities of the Concerned Member States of the marketing authorization of a medicinal product by the competent authorities of other Reference Member States. The holder of a national marketing authorization granted by a Reference Member State may submit an application to the competent authority of a Concerned Member State requesting that this authority mutually recognize the marketing authorization delivered by the competent authority of the Reference Member State.

Similar to accelerated approval regulations in the U.S., conditional marketing authorizations can be granted in the E.U. by the European Commission in exceptional circumstances. A conditional marketing authorization can be granted for medicinal products where a number of criteria are fulfilled; i) although comprehensive clinical data referring to the safety and efficacy of the medicinal product have not been supplied, the benefit/risk balance of the product is positive, ii) it is likely that the applicant will be in a position to provide the comprehensive clinical data, iii) unmet medical needs will be fulfilled and iv) the benefit to public health of the immediate availability on the market of the medicinal product concerned outweighs the risk inherent in the fact that additional data are still required. A conditional marketing authorization must be renewed annually. Under the provisions of the conditional marketing authorization for PIXUVRI, we are required to complete a post-marketing study to further investigate the effects of using PIXUVRI in patients who had received prior treatment with rituximab.

Even if a product receives authorization in the E.U., there can be no assurance that reimbursement for such product will be secured on a timely basis or at all. Individual countries comprising the EU member states, rather than the EU, have jurisdiction across the region over patient reimbursement or pricing matters. Therefore, we will need to expend significant effort and expense to establish and maintain reimbursement arrangements in the various countries

comprising the E.U. and may never succeed in obtaining widespread reimbursement arrangements therein.

The national authorities of the individual E.U. Member States are free to restrict the range of medicinal products for which their national health insurance systems provide reimbursement and to control the prices and/or reimbursement of medicinal products for human use. Some E.U. Member States adopt policies according to which a specific price or level of reimbursement is approved for the medicinal product. Other E.U. Member States adopt a system of direct or indirect controls on the profitability of the company placing the medicinal product on the market, including volume-based arrangements and reference pricing mechanisms.

Health Technology Assessment, or HTA, of medicinal products is becoming an increasingly common part of the pricing and reimbursement procedures in some E.U. Member States. These E.U. Member States include the U.K, France, Germany and Sweden. The HTA process, which is governed by the national laws of these countries, is the procedure according to which the assessment of the public health impact, therapeutic impact and the economic and societal impact of use of a given medicinal product in the national healthcare systems of the individual country is conducted. The extent to which pricing and reimbursement decisions are influenced by the HTA of the specific medicinal product vary between E.U. Member States.

Post-Approval Regulation

Similarly to the U.S., both marketing authorization holders and manufacturers of medicinal products are subject to comprehensive regulatory oversight by the EMA and the competent authorities of the individual E.U. Member States both before and after grant of the manufacturing and marketing authorizations. Failure by us or by any of our third party partners, including suppliers, manufacturers and distributors to comply with E.U. laws and the related national laws of individual E.U. Member States governing the conduct of clinical trials, manufacturing approval, marketing authorization of medicinal products and marketing of such products, both before and after grant of marketing authorization, may result in administrative, civil or criminal penalties. These penalties could include delays or refusal to authorize the conduct of clinical trials or to grant marketing authorization, product withdrawals and recalls, product seizures, suspension, withdrawal or variation of the marketing authorization, total or partial suspension of production, distribution, manufacturing or clinical trials, operating restrictions, injunctions, suspension of licenses, fines and criminal penalties.

The holder of an E.U. marketing authorization for a medicinal product must also comply with E.U. pharmacovigilance legislation and its related regulations and guidelines, which entail many requirements for conducting pharmacovigilance, or the assessment and monitoring of the safety of medicinal products. These rules can impose on central marketing authorization holders for medicinal products the obligation to conduct a labor intensive collection of data regarding the risks and benefits of marketed products and to engage in ongoing assessments of those risks and benefits, including the possible requirement to conduct additional clinical studies, which may be time consuming and expensive and could impact our profitability. Non-compliance with such obligations can lead to the variation, suspension or withdrawal of the marketing authorization for the product or imposition of financial penalties or other enforcement measures. In the E.U., PIXUVRI's label includes an inverted black triangle, which indicates that it is subject to additional monitoring, as a condition of authorization of PIXUVRI.

The manufacturing process for medicinal products in the E.U. is highly regulated and regulators may shut down manufacturing facilities that they believe do not comply with regulations. Manufacturing requires a manufacturing authorization, and the manufacturing authorization holder must comply with various requirements set out in the applicable E.U. laws, regulations and guidance, including Directive 2001/83/EC, Directive 2003/94/EC, Regulation (EC) No 726/2004 and the European Commission Guidelines for Good Manufacturing Practice. These requirements include compliance with E.U. cGMP standards when manufacturing medicinal products and active pharmaceutical ingredients, including the manufacture of active pharmaceutical ingredients outside of the E.U. with the intention to import the active pharmaceutical ingredients into the E.U. Similarly, the distribution of medicinal products into and within the E.U. is subject to compliance with the applicable E.U. laws, regulations and guidelines, including the requirement to hold appropriate authorizations for distribution granted by the competent authorities of the E.U. Member States.

We and our third party manufacturers are subject to cGMP, which are extensive regulations governing manufacturing processes, stability testing, record keeping and quality standards as defined by the EMA, the competent authorities of E.U. Member States and other regulatory authorities. The EMA reviews Periodic Safety Update Reports for medicinal products authorized in the E.U. If the EMA has concerns that the risk benefit profile of a product has varied, it can adopt an opinion advising that the existing marketing authorization for the product be suspended or varied and can advise that the marketing authorization holder be obliged to conduct post-authorization safety studies. The EMA opinion is submitted for approval by the European Commission. Failure by the marketing authorization holder to fulfill the obligations for which the approved opinion provides can undermine the on-going validity of the marketing authorization.

Sales and Marketing Regulations

In the E.U., the advertising and promotion of our products are subject to E.U. Member States' laws governing promotion of medicinal products, interactions with physicians, misleading and comparative advertising and unfair

commercial practices. In addition, other legislation adopted by individual E.U. Member States may apply to the advertising and promotion of medicinal products. These laws require that promotional materials and advertising in relation to medicinal products comply with the product's Summary of Product Characteristics, or SmPC, as approved by the competent authorities. Promotion of a medicinal product that does not comply with the SmPC is considered to constitute off-label promotion. The off-label promotion of medicinal products is prohibited in the E.U.. The applicable laws at E.U. level and in the individual E.U. Member States also prohibit the direct-to-consumer advertising of prescription-only medicinal products. Violations of the rules governing the promotion of medicinal products in the E.U. could be penalized by administrative measures, fines and imprisonment. These laws may further limit or restrict the advertising and promotion of our products to the general public and may also impose limitations on our promotional activities with health care professionals.

Anti-Corruption Legislation

Our business activities outside of the U.S. are subject to anti-bribery or anti-corruption laws, regulations, industry self-regulation codes of conduct and physicians' codes of professional conduct or rules of other countries in which we operate, including the U.K. Bribery Act of 2010.

Interactions between pharmaceutical companies and physicians are also governed by strict laws, regulations, industry self-regulation codes of conduct and physicians' codes of professional conduct developed at both E.U. level and in the individual E.U. Member States. The provision of benefits or advantages to physicians to induce or encourage the prescription, recommendation, endorsement, purchase, supply, order or use of medicinal products is prohibited in the E.U.. Violation of these laws could result in substantial fines and imprisonment. Payments made to physicians in certain E.U. Member States also must be publicly disclosed. Moreover, agreements with physicians must often be the subject of prior notification and approval by the physician's employer, his/her competent professional organization, and/or the competent authorities of the individual E.U. Member States. Failure to comply with these requirements could result in reputational risk, public reprimands, administrative penalties, fines or imprisonment.

Data Privacy and Protection

Data protection laws and regulations have been adopted at E.U. level with related implementing laws in individual E.U. Member States which impose significant compliance obligations. For example, the E.U. Data Protection Directive, as implemented into national laws by the E.U. Member States, imposes strict obligations and restrictions on the ability to collect, analyze and transfer personal data, including health data from clinical trials and adverse event reporting.

Furthermore, there is a growth towards the public disclosure of clinical trial data in the E.U. which also adds to the complexity of processing health data from clinical trials. Such public disclosure obligations are provided in the new E.U. Clinical Trials Regulation, EMA disclosure initiatives, and voluntary commitments by industry. Data protection authorities from the different E.U. Member States may interpret the E.U. Data Protection Directive and national laws differently, which adds to the complexity of processing personal data in the E.U., and guidance on implementation and compliance practices are often updated or otherwise revised. Failing to comply with these laws could lead to government enforcement actions and significant penalties against us, and adversely impact our operating results. Apart from exceptional circumstances, the E.U. Data Protection Directive prohibits the transfer of personal data to countries outside of the European Economic Area, that are not considered by the European Commission to provide an adequate level of data protection, including the U.S.

Consequences of Non-Compliance

Failure to comply with applicable requirements may subject us to administrative or judicial sanctions, such as clinical holds, refusal of regulatory authorities to approve or authorize pending product applications, warning letters, product recalls, product seizures, total or partial suspension of production or distribution, injunctions and/or criminal prosecution.

Environmental Regulation

In connection with our research and development activities, we are subject to federal, state and local laws, rules, regulations and policies, both internationally and domestically, governing the use, generation, manufacture, storage, air emission, effluent discharge, handling, treatment, transportation and disposal of certain materials, biological specimens and wastes and employee safety and health matters. Although we believe that we have complied with these laws, regulations and policies in all material respects and have not been required to take any significant action to correct any noncompliance, we may be required to incur significant costs to comply with environmental and health and safety regulations in the future. Our research and development involves the controlled use of hazardous materials, including, but not limited to, certain hazardous chemicals and radioactive materials. Although we believe that our safety procedures for handling and disposing of such materials comply with applicable law and regulations, the risk of accidental contamination or injury from these materials cannot be eliminated. In the event of such an accident, we could be held liable for any damages that result and any such liability not covered by insurance could exceed our resources. See the risk factor, "Since we use hazardous materials in our business, we may be subject to claims relating to improper handling, storage or disposal of these materials." in Part I, Item 1A, "Risk Factors" of this Annual Report on

Form 10-K for additional information regarding the risks and uncertainties we face due to the use of hazardous materials.

Employees

As of December 31, 2014, we employed 125 individuals in the U.S., including two employees at our majority-owned subsidiary Aequus Biopharma, Inc., or Aequus, and seven in Europe. Our U.S. and U.K. employees do not have a collective bargaining agreement. Two employees in Italy are subject to a collective bargaining agreement. We believe our relations with our employees are good.

Corporate Information

We were incorporated in Washington in 1991. In May 2014, we changed our name from “Cell Therapeutics, Inc.” to “CTI BioPharma Corp.” We completed our initial public offering in 1997 and our shares are listed on The NASDAQ Capital Market in the U.S. and the Mercato Telematico Azionario, or the MTA in Italy where our symbol is CTIC. Our principal executive offices are located at 3101 Western Avenue, Suite 600, Seattle, Washington 98121. Our telephone number is (206) 282-7100. Our website address is <http://www.ctibiopharma.com>. We may post information that is important to investors on our website. However, information found on our website is not incorporated by reference into this Annual Report on Form 10-K. “CTI BioPharma”, “PIXUVRI” and “Opaxio” are our proprietary marks. All other product names, trademarks and trade names referred to in this Annual Report on Form 10-K are the property of their respective owners. We make available free of charge on our website our Annual Reports on Form 10-K, Quarterly Reports on Form 10-Q, Current Reports on Form 8-K and other filings pursuant to Section 13(a) or 15(d) of the Securities Exchange Act of 1934, as amended, or the Exchange Act, as soon as reasonably practicable after each is electronically filed with, or furnished to, the SEC.

In addition, you may review a copy of this Annual Report on Form 10-K, including exhibits and any schedule filed herewith, and obtain copies of such materials at prescribed rates, at the SEC’s Public Reference Room at 100 F Street, N.E., Washington, D.C. 20549. You may obtain information on the operation of the Public Reference Room by calling the SEC at 1-800-SEC-0330. The SEC maintains a website (<http://www.sec.gov>) that contains reports, proxy and information statements and other information regarding registrants, including the Company, that file electronically with the SEC.

Item 1A. Risk Factors

This Annual Report on Form 10-K contains forward-looking statements that involve risks and uncertainties. The occurrence of any of the risks described below and elsewhere in this document, including the risk that our actual results may differ materially from those anticipated in these forward-looking statements, could materially adversely affect our business, financial condition, operating results or prospects and the trading price of our securities. Additional risks and uncertainties that we do not presently know or that we currently deem immaterial may also harm our business, financial condition, operating results and prospects and the trading price of our securities.

We will need to raise additional funds to operate our business, but additional funds may not be available on acceptable terms, or at all. Any inability to raise required capital when needed could harm our liquidity, financial condition, business, operating results and prospects.

We have substantial operating expenses associated with the development of our compounds and the commercialization of PIXUVRI, and we have significant contractual payment obligations. Our available cash and cash equivalents were \$70.9 million as of December 31, 2014. We believe that our present financial resources, together with additional milestone payments projected to be received under certain of our contractual agreements, our ability to control costs and expected net sales of PIXUVRI, will only be sufficient to fund our operations through mid-third quarter of 2015. Cash forecasts and capital requirements are subject to change as a result of a variety of risks and uncertainties. Changes in manufacturing, developments in and expenses associated with our research and development activities, acquisitions of compounds or other assets, any expansion of our sales and marketing organization for PIXUVRI, regulatory approval developments, ability to consummate appropriate collaborations for development and commercialization activities, litigation and other disputes, competitive market developments and other unplanned business developments may consume capital resources earlier than planned. Additionally, we may not receive anticipated milestone payments or achieve projected net sales from PIXUVRI. Due to these and other factors, our forecast for the period for which we will have sufficient resources to fund our operations, as well as any other operational or business projection we have disclosed, or may, from time to time, disclose, may fail.

As of December 31, 2014, we have \$18.5 million outstanding under our senior secured term loan agreement, and we are required to make monthly interest plus principal payments in the aggregate amount of approximately \$0.9 million through October 1, 2016. Such borrowings are secured by a first priority security interest on substantially all of our personal property except our intellectual property and subject to certain other exceptions. In addition, the senior secured term loan agreement, under which we have no additional borrowing capacity, requires us to comply with restrictive covenants, including those that limit our operating flexibility and ability to borrow additional funds. A failure to make a required loan payment or an uncured covenant breach could lead to an event of default, and in such case, all amounts then outstanding may become due and payable immediately.

We will need to acquire additional funds in order to operate our business. We may seek to raise such capital through public or private equity financings, partnerships, collaborations, joint ventures, disposition of assets, debt financings or restructurings, bank borrowings or other sources of financing. However, our ability to do so is subject to a number of risks, uncertainties, constraints and consequences, including:

- our ability to raise capital through the issuance of additional shares of our common stock or convertible securities is restricted by the limited number of our residual authorized shares, the potential difficulty of obtaining shareholder approval to increase authorized shares and the restrictive covenants under our senior secured term loan agreement;
- issuance of equity-based securities will dilute the proportionate ownership of existing shareholders;
- our ability to obtain further funds from any potential loan arrangements is limited by our existing senior secured term loan agreement;
- certain financing arrangements may require us to relinquish rights to various assets and/or impose more restrictive terms than any of our existing or past arrangements; and
- we may be required to meet additional regulatory requirements, and we may be subject to certain contractual limitations, which may increase our costs and harm our ability to obtain funding.

For these and other reasons, additional funding may not be available on favorable terms or at all. If we fail to obtain additional capital when needed, we may be required to delay, scale back or eliminate some or all of our research and development programs, reduce our selling, general and administrative expenses, be unable to attract and retain highly qualified personnel, refrain from making our contractually required payments when due (including debt payments) and/or be forced to cease operations, liquidate our assets and possibly seek bankruptcy protection. Any of these consequences could harm our business, financial condition, operating results and prospects.

We received an audit report for the years ended December 31, 2007 through December 31, 2011 and December 31, 2014 containing an explanatory paragraph on our consolidated financial statements raising substantial doubt as to our ability to continue as a going concern.

We received an audit report for each of the years ended December 31, 2007 through December 31, 2011 and December 31, 2014 containing an explanatory paragraph on our consolidated financial statements raising substantial doubt as to our ability to continue as a going concern. The inclusion of a going concern explanatory paragraph may negatively impact the trading price of our common stock and make it more difficult, time consuming or expensive to obtain necessary financing. In the event our operations were to cease, you would suffer a complete loss of your investment in our securities.

We expect to continue to incur net losses, and we may never achieve profitability.

We were incorporated in 1991 and have incurred a net operating loss every year since our formation. As of December 31, 2014, we had an accumulated deficit of \$2.0 billion, and we expect to continue to incur net losses. As part of our business plan, we will need to continue to conduct research, development, testing and regulatory compliance activities with respect to our compounds and ensure the procurement of manufacturing and drug supply services, the costs of which, together with projected general and administrative expenses, is expected to result in operating losses for the foreseeable future. There can be no assurances that we will ever achieve profitability.

If our development and commercialization collaborations are not successful, or if we are unable to enter into additional collaborations, we may not be able to effectively develop and/or commercialize the applicable compound(s), which could have a material adverse effect on our business.

Our business is heavily dependent on the success of our development and commercialization collaborations. In particular, under the Servier Agreement and the Baxter Agreement, we rely heavily on Servier and Baxter, respectively, to collaborate with us to develop and commercialize PIXUVRI and pacritinib. As a result of our dependence on our relationships with Servier and Baxter, the success or commercial viability of PIXUVRI and pacritinib is, to a certain extent, beyond our control. We are subject to a number of specific risks associated with our dependence on our collaborative relationship with Servier and Baxter, including the following: possible disagreements as to the timing, nature and extent of development plans for the respective compound, including clinical trials or regulatory approval strategy; changes in their respective personnel who are key to the collaboration efforts; any changes in their respective business strategies adverse to our interests; possible disagreements regarding ownership of proprietary rights; and the possibility that Servier or Baxter could elect to terminate their respective agreements with us pursuant to certain “at-will” termination clauses or otherwise breach their respective agreements with us. Furthermore, the contingent financial returns under our collaborations with Servier and Baxter depend in large part on the achievement of development and commercialization milestones and the ability to generate applicable product sales to trigger royalty payments. Therefore, our success, and any associated future financial returns to us and our investors, will depend in large part on the performance of each of Servier and Baxter. If our existing collaborations fail, or if we do not successfully enter into additional collaborations when needed, we may be unable to further develop and commercialize our compounds, generate revenues to sustain or grow our business or achieve profitability, which would harm our business, financial condition, operating results and prospects.

Compounds that appear promising in research and development may fail to reach later stages of development for a number of reasons, including, among others, that clinical trials may take longer to complete than expected or may not be completed at all, and top-line or preliminary clinical trial data reports may ultimately differ from actual results once existing data are more fully evaluated.

Successful development of anti-cancer and other pharmaceutical products is highly uncertain, and obtaining regulatory approval to market drugs to treat cancer is expensive, difficult and speculative. Compounds that appear promising in research and development may fail to reach later stages of development for several reasons, including,

but not limited to:

- delay or failure in obtaining necessary U.S. and international regulatory approvals, or the imposition of a partial or full regulatory hold on a clinical trial;
- difficulties in formulating a compound, scaling the manufacturing process and obtaining manufacturing approval, pricing, reimbursement issues or other factors that may make the product uneconomical to commercialize;
- production problems, such as the inability to obtain raw materials or supplies satisfying acceptable standards for the manufacture of our products, equipment obsolescence, malfunctions or failures, product quality/contamination problems or changes in regulations requiring manufacturing modifications;
- inefficient cost structure of a compound compared to alternative treatments;
- obstacles resulting from proprietary rights held by others with respect to a compound, such as patent rights;

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- lower than anticipated rates of patient enrollment as a result of factors, such as the number of patients with the relevant conditions, the proximity of patients to clinical testing centers, eligibility criteria for tests and competition with other clinical testing programs;
- preclinical or clinical testing requiring significantly more time than expected, resources or expertise than originally expected and inadequate financing, which could cause clinical trials to be delayed or terminated;
- failure of clinical testing to show potential products to be safe and efficacious, and failure to demonstrate desired safety and efficacy characteristics in human clinical trials;
- suspension of a clinical trial at any time by us, an applicable collaboration partner or a regulatory authority on the basis that the participants are being exposed to unacceptable health risks or for other reasons;
- delays in reaching or failing to reach agreement on acceptable terms with prospective clinical research organizations, or CROs, and trial sites; and
- failure of third parties, such as CROs, academic institutions, collaborators, cooperative groups and/or investigator sponsors, to conduct, oversee and monitor clinical trials and results.

In addition, while we have reported top-line data for PERSIST-1 in this Annual Report on Form 10-K and may report additional top-line data for other trials from time to time, such data are based on a preliminary analysis of then-available efficacy and safety data, and such findings and conclusions are subject to change following a more comprehensive review of the data related to the particular study or trial. Top-line or preliminary data is based on important assumptions, estimations, calculations and information then available to us to the extent we have, at the time of such reporting, had an opportunity to fully and carefully evaluate such information in light of all surrounding facts, circumstances, recommendations and analyses. As a result, top-line results observed to date may differ from future results, or different conclusions or considerations may qualify such results once existing data has been more fully evaluated. In addition, third parties, including regulatory agencies, may not accept or agree with our assumptions, estimations, calculations or analyses or may interpret or weigh the importance of data differently, which could impact the value of the particular program, the approvability or commercialization of the particular compound and our business in general.

If the development of our compounds is delayed or fails, or if top-line or preliminary clinical trial data reported differ from actual results, our development costs may increase and the ability to commercialize our compounds may be harmed, which could harm our business, financial condition, operating results or prospects.

We or our collaboration partners may not obtain or maintain the regulatory approvals required to develop or commercialize some or all of our compounds.

We are subject to rigorous and extensive regulation by the FDA in the U.S. and by comparable agencies in other jurisdictions, including the EMA in the E.U. Pacritinib and our other product candidates are currently in research or development and, other than conditional marketing authorization for PIXUVRI in the E.U., we have not received marketing approval for our compounds. Our products may not be marketed in the U.S. until they have been approved by the FDA and may not be marketed in other jurisdictions until they have received approval from the appropriate foreign regulatory agencies. Each product candidate requires significant research, development and preclinical testing and extensive clinical investigation before submission of any regulatory application for marketing approval. Obtaining regulatory approval requires substantial time, effort and financial resources, and we may not be able to obtain approval of any of our products on a timely basis, or at all. The number and focus of preclinical and clinical trials that will be required for approval by the FDA, the EMA or any other foreign regulatory agency varies depending on the compound, the disease or condition that the compound is designed to address and the regulations applicable to any particular compound. Preclinical and clinical data can be interpreted in different ways, which could delay, limit or preclude regulatory approval. The FDA, the EMA and other foreign regulatory agencies can delay, limit or deny approval of a compound for many reasons, including, but not limited to:

- a compound may not be shown to be safe or effective;
- clinical trial results may be negative or inconclusive, or adverse medical events may occur during a clinical trial;
-

such regulatory agencies may not approve the manufacturing process of a compound and may interpret data from pre-clinical and clinical trials in different ways than we do;

- a compound may fail to comply with regulatory requirements; or
- such regulatory agencies might change their approval policies or adopt new regulations.

If our compounds are not approved quickly enough to provide net revenues to defray our operating expenses, our business, financial condition, operating results and prospects could be harmed.

Even if our compounds are successful in clinical trials and receive regulatory approvals, we or our collaboration partners may not be able to successfully commercialize them.

The development and ongoing clinical trials for our compounds may not be successful and, even if they are, the resulting products may never be successfully developed into commercial products. Even if we are successful in our clinical trials and in obtaining other regulatory approvals, the respective products may not reach or remain in the market for a number of reasons including:

- they may be found ineffective or cause harmful side effects;
- they may be difficult to manufacture on a scale necessary for commercialization;
- they may be uneconomical to produce;
- we may fail to obtain reimbursement approvals or pricing that is cost effective for patients as compared to other available forms of treatment or that covers the cost of production and other expenses;
- they may not compete effectively with existing or future alternatives;
- we may be unable to develop commercial operations and to sell marketing rights;
- they may fail to achieve market acceptance; or
- we may be precluded from commercialization of a product due to proprietary rights of third parties.

In particular, with respect to the commercialization of PIXUVRI and the future potential commercialization of pacritinib, we will be heavily dependent on our collaboration partners, Servier and Baxter, respectively. The failure of Servier or Baxter (or any other applicable collaboration partner) to fulfill its respective commercialization obligations with respect to a compound, or the occurrence of any of the events in the list above, could adversely affect the commercialization of our products. If we fail to commercialize products or if our future products do not achieve significant market acceptance, we will not likely generate significant revenues or become profitable.

The pharmaceutical business is subject to increasing government price controls and other restrictions on pricing, reimbursement, and access to drugs, which could adversely affect our future revenues and profitability.

To the extent our products are developed, commercialized and successfully introduced to market, they may not be considered cost-effective and third party or government reimbursement might not be available or sufficient. Globally, governmental and other third party payors are becoming increasingly aggressive in attempting to contain healthcare costs by strictly controlling, directly or indirectly, pricing and reimbursement and, in some cases, limiting or denying coverage altogether on the basis of a variety of justifications, and we expect pressures on pricing and reimbursement from both governments and private payors inside and outside the U.S. to continue. In the U.S., we are subject to substantial pricing, reimbursement and access pressures from state Medicaid programs, private insurance programs and pharmacy benefit managers, and implementation of U.S. health care reform legislation is increasing these pricing pressures. The Patient Protection and Affordable Care Act instituted comprehensive health care reform, which includes provisions that, among other things, reduce and/or limit Medicare reimbursement, require all individuals to have health insurance (with limited exceptions) and impose new and/or increased taxes. In almost all European markets, pricing and choice of prescription pharmaceuticals are subject to governmental control. Therefore, the price of our products and their reimbursement in Europe is and will be determined by national regulatory authorities. Reimbursement decisions from one or more of the European markets may impact reimbursement decisions in other European markets. A variety of factors are considered in making reimbursement decisions, including whether there is sufficient evidence to show that treatment with the product is more effective than current treatments, that the product represents good value for money for the health service it provides and that treatment with the product works at least as well as currently available treatments. The continuing efforts of government and insurance companies, health maintenance organizations and other payors of healthcare costs to contain or reduce costs of health care may affect our future revenues and profitability or those of our potential customers, suppliers and collaborative partners, as well as the availability of capital.

We may never be able to generate significant product revenues from the sale of PIXUVRI.

We anticipate that, for at least the next several years, our ability to generate revenues and become profitable will depend, in part, on our ability and that of our collaborator, Servier, to successfully commercialize our only marketed product, PIXUVRI. As disclosed elsewhere herein, PIXUVRI is not approved for marketing in the U.S., is presently available only in a limited number of countries and is reimbursed in even fewer countries.

In addition, the successful commercialization of PIXUVRI depends heavily on the ability to obtain and maintain favorable reimbursement rates for users of PIXUVRI, as well as on various additional factors, including, without limitation, the ability to:

- obtain an annual renewal of our conditional marketing authorization for PIXUVRI;
- increase demand for and sales of PIXUVRI and obtain greater acceptance of PIXUVRI by physicians and patients;
- establish and maintain agreements with wholesalers and distributors on reasonable terms;
- maintain, and where necessary, enter into additional, commercial manufacturing arrangements with third parties, cost-effectively manufacture necessary quantities and secure distribution, managerial and other capabilities; and
- further develop and maintain a commercial organization to market PIXUVRI.

If we are unable to successfully commercialize PIXUVRI as planned, our business, financial condition, operating results and prospects could be harmed.

Post-approval or authorization regulatory reviews and obligations often result in significant expense and marketing limitations, and any failure to satisfy such ongoing obligations, including, in particular, our post-authorization commitment trial for PIXUVRI, could negatively affect our business, financial condition, operating results or prospects.

Even if a product receives regulatory approval or authorization, as applicable, we are and will continue to be subject to numerous regulations and statutes regulating the manner of obtaining reimbursement for and selling the product, including limitations on the indicated uses for which a product may be marketed. Approved or authorized products, including PIXUVRI, are subject to extensive labeling, packaging, adverse event reporting, storage, advertising, promotion and record-keeping regulations. Regulatory authorities may also impose new restrictions on continued product marketing or may require the withdrawal of a product from the market if adverse events of unanticipated severity or frequency are discovered following approval. In addition, regulatory agencies may impose post-approval/post-authorization clinical trials, such as our ongoing PIX306 study of PIXUVRI required by the EMA. We cannot predict the outcome of PIX306 or whether we will be able to complete the associated requirements in a timely manner. If we are unable to submit the requisite PIX306 clinical study report by the due date in November 2016 or are otherwise unable to satisfy all applicable requirements, our conditional marketing authorization for PIXUVRI may be revoked. A revocation of PIXUVRI's or any other product's approval or authorization or any other failure to maintain applicable regulatory approvals would result in the respective product being withdrawn from the market, product seizures, monetary penalties or possible criminal prosecution, which could negatively affect our business, financial condition, operating results or prospects.

We may be unable to obtain a quorum for meetings of our shareholders or obtain requisite shareholder approval and, consequently, be unable to take certain corporate actions.

Failure to meet the requisite quorum or obtain requisite shareholder approval can prevent us from raising capital through equity financing or otherwise taking certain actions that may be in our best interest and that of our shareholders. We have experienced such difficulties in the past.

A portion of our common shares are held by Italian institutions and, under Italian laws and regulations, it is difficult to communicate with the beneficial holders of those shares to obtain votes. In recent years, certain depository banks in Italy holding shares of our common stock have facilitated book-entry transfers of their share positions at Monte Titoli

to their U.S. correspondent bank, who would then transfer the shares to an account of the Italian bank at a U.S. broker-dealer that is an affiliate of that bank. Certain of the banks we contacted to facilitate these arrangements agreed to make the share transfers pursuant to these arrangements as of the record date of the shareholder meeting, subject to the relevant beneficial owner being given notice before such record date and taking no action to direct the voting of such shares. Obtaining a quorum and necessary shareholder approvals at shareholder meetings may depend in part upon the willingness of the Italian depository banks to continue participating in the custody transfer arrangements, and we cannot be assured that those banks that have participated in the past will continue to do so in the future.

As a result of the foregoing or for other reasons, we may be unable to obtain a quorum at annual or special meetings of shareholders. Even if we are able to obtain a quorum at our shareholder meetings, we may not obtain enough votes to approve matters to be resolved upon at those meetings. Any failure to obtain a quorum or the requisite vote on a proposal in question could harm us.

We could fail in financing efforts if we fail to receive shareholder approval when needed.

We are required under the NASDAQ Marketplace Rules to obtain shareholder approval for any issuance of additional equity securities that would comprise more than 20 percent of the total shares of our common stock outstanding before the issuance of such securities sold at a discount to the greater of book or market value in an offering that is not deemed to be a “public offering” by the NASDAQ Marketplace Rules, as well as under certain other circumstances. We have in the past and may in the future issue additional equity securities that would comprise more than 20 percent of the total shares of our common stock outstanding in order to fund our operations. However, we might not be successful in obtaining the required shareholder approval for any future issuance that requires shareholder approval pursuant to applicable rules and regulations, particularly in light of difficulties we have had in the past in obtaining a quorum and obtaining the requisite vote. If we are unable to obtain financing or our financing options are limited due to shareholder approval difficulties, such failure may harm our ability to continue operations.

We are subject to Italian regulatory requirements, which limit our ability to issue additional shares of our common stock, could result in administrative and other challenges and additional expenses and/or could limit our ability to undertake other business initiatives.

Because our common stock is traded on the MTA in Italy, we are required to also comply with the rules and regulations of CONSOB and the Borsa Italiana, which regulate companies listed on Italy’s public markets. Compliance with Italian regulatory requirements may delay additional issuances of our common stock or other business initiatives. Under Italian law, we must publish a registration document, securities note and summary (which jointly compose a prospectus) that have to be approved by CONSOB prior to issuing common stock that is equal to or exceeds, in any twelve-month period, 10 percent of the number of shares of our common stock outstanding at the beginning of that period, subject to certain exceptions. If we are unable to obtain and maintain a registration document, securities note or summary to cover general financing efforts under Italian law, we may be required to raise money using alternative forms of securities. For example, we have issued convertible preferred stock in numerous prior offerings and may in the future issue convertible securities; the common stock resulting from the conversion of such securities, subject to current provisions of European Directive No. 71/2003 and according to the current interpretations of the Committee of European Securities Regulators, is not subject to the 10 percent limitation imposed by E.U. and Italian law. However, this exception to the prospectus requirement could change or cease to be available as a result of changes in regulations, interpretive positions, policies or otherwise. Any such change may increase compliance costs or limit our ability to issue securities. Compliance with these regulations and responding to periodic information requests from Borsa Italiana and CONSOB requires us to devote additional time and resources to regulatory compliance matters and to incur additional expenses of engaging additional outside counsel, accountants and other professional advisors. Actual or alleged failure to comply with Italian regulators can also subject us to regulatory investigations and fines or other sanctions from time to time. For more information on a current investigation, see Part I, Item 3, Legal Proceedings.

Any of such regulatory requirements of CONSOB and the Borsa Italiana could result in administrative and other challenges and additional expenses, limit our ability to undertake other business initiatives and negatively affect our business, financial condition, operating results and prospects.

We will incur a variety of costs for, and may never realize the anticipated benefits of, acquisitions, collaborations or other strategic transactions.

We evaluate and undertake acquisitions, collaborations and other strategic transactions from time to time. The process of negotiating these transactions, as well as integrating any acquisitions and implementing any strategic alliances, may result in operating difficulties and expenditures. In addition, these transactions may require significant management attention that would otherwise be available for ongoing development of our business, whether or not any such transaction is ever consummated. These undertakings could also result in potentially dilutive issuances of equity securities, including common stock and preferred stock, the incurrence of debt, contingent liabilities and/or

amortization expenses related to intangible assets, and we may never realize the anticipated benefits. In addition, following the consummation of a transaction, our results of operations and the market price of our common stock may be affected by factors different from those that affected our results of operations and the market price of our common stock prior to such acquisition. Any of the foregoing consequences resulting from transactions of the type described above could harm our business, financial condition, operating results or prospects.

We may be subject to fines, penalties, injunctions and other sanctions if we are deemed to be promoting the use of our products for non-FDA-approved, or off-label, uses.

Our business and future growth depend on the development, ultimate sale and use of products that are subject to FDA, EMA and or other regulatory agencies regulation, clearance and approval. Under the U.S. Federal Food, Drug, and Cosmetic Act and other laws, we are prohibited from promoting our products for off-label uses. This means that in the U.S., we may not make claims about the safety or effectiveness of our products and may not proactively discuss or provide information on the use of our products, except as allowed by the FDA.

Government investigations concerning the promotion of off-label uses and related issues are typically expensive, disruptive and burdensome, generate negative publicity and may result in fines or payments of settlement awards. For example, in April 2007, we paid a civil penalty of \$10.6 million and entered into a settlement agreement with the U.S. Attorney's Office for the Western District of Washington arising out of their investigation into certain of our prior marketing practices relating to TRISENOX, which was divested to Cephalon in July 2005. As part of that settlement agreement and in connection with the acquisition of Zevalin, we also entered into a corporate integrity agreement with the Office of the Inspector General, Health and Human Services, which required us to establish a compliance committee and compliance program and adopt a formal code of conduct. If our promotional activities are found to be in violation of applicable law or if we agree to a settlement in connection with an enforcement action, we would likely face significant fines and penalties and would likely be required to substantially change our sales, promotion, grant and educational activities.

A failure to comply with the numerous laws and regulations that govern our business, including those related to cross-border conduct, healthcare fraud and abuse, anti-corruption and false claims and the protection of health information, could result in substantial penalties and prosecution.

We are subject to risks associated with doing business outside of the U.S., which exposes us to complex foreign and U.S. regulations. For example, we are subject to regulations imposed by the Foreign Corrupt Practices Act, or FCPA, and other anti-corruption laws that generally prohibit U.S. companies and their intermediaries from offering, promising, authorizing or making improper payments to foreign government officials for the purpose of obtaining or retaining business. The SEC and U.S. Department of Justice have increased their enforcement activities with respect to the FCPA. Internal control policies and procedures and employee training and compliance programs that we have implemented to deter prohibited practices may not be effective in prohibiting our employees, contractors or agents from violating or circumventing our policies and the law.

In addition, we are subject to various state and federal fraud and abuse laws, including, without limitation, the federal Anti-Kickback Statute and federal False Claims Act. There are similar laws in other countries. These laws may impact, among other things, the sales, marketing and education programs for our products. The federal Anti-Kickback Statute prohibits persons from knowingly and willingly soliciting, offering, receiving or providing remuneration, directly or indirectly, in exchange for or to induce either the referral of an individual, or the furnishing or arranging for a good or service, for which payment may be made under a federal healthcare program. The federal False Claims Act prohibits persons from knowingly filing, or causing to be filed, a false claim to, or the knowing use of false statements to obtain payment from the federal government. Suits filed under the False Claims Act can be brought by any individual on behalf of the government and such individuals, commonly known as "whistleblowers," may share in any amounts paid by the entity to the government in fines or settlement. Many states have also adopted laws similar to the federal Anti-Kickback Statute and False Claims Act.

We may also be subject to the Health Insurance Portability and Accountability Act of 1996, as amended by the Health Information Technology for Economic and Clinical Health Act and their respective implementing regulations, or HIPAA, which established uniform standards for certain "covered entities" (healthcare providers, health plans and healthcare clearinghouses) governing the conduct of certain electronic healthcare transactions and protecting the security and privacy of protected health information. Among other things, HIPAA's privacy and security standards are directly applicable to "business associates" — independent contractors or agents of covered entities that create, receive, maintain or transmit protected health information in connection with providing a service for or on behalf of a covered entity. In addition to possible civil and criminal penalties for violations, state attorneys general are authorized to file civil actions for damages or injunctions in federal courts to enforce HIPAA 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.

We are unable to predict whether we could be subject to actions under any of the foregoing or similar laws and regulations, or the impact of such actions. If we were to be found to be in violation of applicable laws or regulations, we may be subject to penalties, including civil and criminal penalties, damages, fines, exclusion from government healthcare reimbursement programs and the curtailment or restructuring of our operations, all of which could have a material adverse effect on our business and results of operations.

We are dependent on third party service providers for a number of critical operational activities including, in particular, for clinical trial activities and for the manufacture, testing and distribution of our compounds and associated supply chain operations. Any failure or delay in these undertakings by third parties could harm our business.

Our business is dependent on the performance by third parties of their responsibilities under contractual relationships. In particular, we depend on medical institutions and CROs (together with their respective employees, subcontractors and other agents, as applicable) to conduct clinical trials and associated activities in compliance with Good Clinical Practice, or GCP, and in accordance with our timelines, expectations and requirements. To the extent any such third parties are delayed in achieving or fail to meet our clinical trial enrollment expectations, fail to conduct our trials in accordance with GCP or study protocol or otherwise take actions outside of our control or without our consent, our business may be harmed. In addition, we conduct clinical trials in foreign countries, which subjects us to additional risks and challenges, including, in particular, as a result of the engagement of foreign medical institutions and foreign CROs, who may be less experienced with regard to regulatory matters applicable to us and may have different standards of medical care.

We also rely heavily on third parties for the manufacture, testing and distribution of our compounds and associated supply chain operations. We do not have internal analytical laboratory or manufacturing facilities to allow the testing or production of drug products in compliance with cGMPs. As a result, we are reliant on third parties to supply us in a timely manner with manufactured products/product candidates. We depend on these third parties to conduct their operations in compliance with cGMPs or similar standards imposed by the U.S. and/or applicable foreign regulatory authorities, including the FDA and EMA. Any of such regulatory authorities may take action against a contract manufacturer who violates cGMPs. Failure of our manufacturers to comply with FDA, EMA or other applicable regulations may cause us to curtail or stop the manufacture of such products until we obtain regulatory compliance. We also rely on third party service providers for certain warehousing, transportation, sales, order processing, distribution and cash collection services. For example, Quintiles Commercial Europe Limited provides a variety of key services to us related to the commercialization of PIXUVRI in certain countries in Europe.

With respect to certain clinical trial operations and steps in the manufacturing and distribution chain of our compounds, we rely on single vendors. The use of single vendors for these core operational activities and the resulting lack of diversification expose us to the risk of an interruption in service related to these single, outside vendors. As a result, our exposure to this concentration risk could harm our business.

If the third parties on which we depend were to default on the performance of their contractual obligations to us or otherwise fail in properly executing their duties on our behalf, including, but not limited to, those relating to the clinical trials, manufacturing, distribution and other core operational activities, our business could be harmed.

We face direct and intense competition from our competitors in the biotechnology and pharmaceutical industries, and we may not compete successfully against them.

Competition in the oncology market is intense and is accentuated by the rapid pace of technological and product development. We anticipate that we will face increased competition in the future as new companies enter the market. Our competitors in the U.S. and elsewhere are numerous and include, among others, major multinational pharmaceutical companies, specialized biotechnology companies and universities and other research institutions. Specifically:

- In Europe, PIXUVRI faces competition from existing treatments for adults with multiply relapsed or refractory aggressive B-cell NHL. For example, patients are currently being treated with bendamustine, oxaliplatin and gemcitabine, although these particular agents do not have regulatory approval in Europe for the foregoing indication. If we were to pursue bringing PIXUVRI to market in the U.S. (which is not currently part of our near-term plan), PIXUVRI would face similar competition.
- If we are successful in bringing pacritinib to market, pacritinib will face competition from ruxolitinib (Jakafi®).
- If we are successful in bringing tosedostat to market, tosedostat will face competition from currently marketed products, such as cytarabine, Dacogen®, Vidaza®, Clolar®, Revlimid® and Thalomid®.
- If we are successful in bringing Opaxio to market, we will face competition from other taxanes, epothilones, and other cytotoxic agents, which inhibit cancer cells by a mechanism similar to taxanes, or similar products such as

paclitaxel and generic forms of paclitaxel, docetaxel, Tarceva®, Avastin®, Alimta®, and Abraxane®. In addition to the specific competitive factors discussed above, new anti-cancer drugs that may be developed and marketed in the future could compete with our various compounds.

Many of our competitors, particularly multinational pharmaceutical companies, either alone or together with their collaborators, have substantially greater financial and technical resources and substantially larger development and marketing teams than us, as well as significantly greater experience than we do in developing, commercializing, manufacturing, marketing and selling products. As a result, products of our competitors might come to market sooner or might prove to be more effective, less expensive, have fewer side effects or be easier to administer than ours. In any such case, sales of PIXUVRI or any potential future product would likely suffer and we might never recoup the significant investments we have made and will continue to make to develop and market these compounds.

If we are unable to in-license or acquire additional product candidates, our future product portfolio and potential profitability could be harmed.

One component of our business strategy is the in-licensing and acquisition of drug compounds developed by other pharmaceutical and biotechnology companies or academic research laboratories. PIXUVRI, pacritinib, tosedostat and Opaxio have all been in-licensed or acquired from third parties. Competition for new, promising compounds and commercial products can be intense. If we are not able to identify future in-licensing or acquisition opportunities and enter into arrangements on acceptable terms, our future product portfolio and potential profitability could be harmed.

If any of our license agreements for intellectual property underlying our compounds are terminated, we may lose the right to develop or market that product.

We have acquired or licensed intellectual property from third parties, including patent applications and patents relating to intellectual property for PIXUVRI, pacritinib and tosedostat. We have also licensed the intellectual property for our drug delivery technology relating to Opaxio, which uses polymers that are linked to drugs known as polymer-drug conjugates. Some of our product development programs depend on our ability to maintain rights under these arrangements. Each licensor has the power to terminate its agreement with us if we fail to meet our obligations under these licenses. We may not be able to meet our obligations under these licenses. If we default under any license agreement, we may lose our right to market and sell any products based on the licensed technology and may be forced to cease operations, liquidate our assets and possibly seek bankruptcy protection. Bankruptcy may result in the termination of agreements pursuant to which we license certain intellectual property rights.

We hold rights under numerous patents that we have acquired or licensed or that protect inventions originating from our research and development, and the expiration of any of these patents may allow our competitors to copy the inventions that are currently protected.

We dedicate significant resources to protecting our intellectual property, which is important to our business. We have filed numerous patent applications in the U.S. and various other countries seeking protection of inventions originating from our research and development, and we have also obtained rights to various patents and patent applications under licenses with third parties and through acquisitions. Patents have been issued on many of these applications. We have pending patent applications or issued patents in the U.S. and foreign countries directed to PIXUVRI, pacritinib, tosedostat, Opaxio and other product candidates. However, the lives of these patents are limited. Patents for the individual products extend for varying periods according to the date of the patent filing or grant and the legal term of patents in the various countries where patent protection is obtained. The patent status of our compounds follows:

- Our PIXUVRI-directed patents currently in force in Europe will begin to expire in late March 2015 through a portion of 2023. Certain of such European patents are also subject to Supplementary Protection Certificates that extend the life of the applicable patents such that they will instead expire from 2020 to 2027. In addition, we are seeking to obtain Supplementary Protection Certificates for certain other of our PIXUVRI-directed European patents that, if obtained, could provide extensions of the applicable patents through 2027. However, no assurances can be made that such extensions will be granted. Our PIXUVRI-directed U.S. patents expired in 2014, and although we have a pending PIXUVRI-directed U.S. patent application (which, if granted, would expire in 2023), we have to date been unable to obtain issuance of a patent for such application (and no assurances can be made that we will ever receive

- such patent). Our PIXUVRI-directed patents outside of Europe and the U.S. expire from 2015 to 2023.
- Our U.S. and various foreign pacritinib-directed patents expire from 2026 through 2029.
 - Our U.S. and various foreign tosedostat-directed patents expire from 2017 to 2018.
 - Our U.S. and various foreign Opaxio-directed patents expire on various dates ranging from 2017 through 2018.
 - Our U.S. and various foreign brostallicin-directed patents expire on various dates ranging between 2017 through 2021.

In the absence of a patent, as in the case of PIXUVRI in the U.S., we will, to the extent possible, need to rely on unpatented technology, know-how and confidential information. Ultimately, the lack or expiration at any given time of a patent to protect our compounds may allow our competitors to copy the underlying inventions and better compete with us.

If we fail to adequately protect our intellectual property, our competitive position and the potential for long-term success could be harmed.

Development and protection of our intellectual property are critical to our business. If we do not adequately protect our intellectual property, competitors may be able to practice our technologies. Our success depends in part on our ability to:

- obtain and maintain patent protection for our products or processes both in the U.S. and other countries;
- protect trade secrets; and
- prevent others from infringing on our proprietary rights.

The patent position of pharmaceutical and biotechnology firms, including ours, generally is highly uncertain and involves complex legal and factual questions. The U.S. Patent and Trademark Office has not established a consistent policy regarding the breadth of claims that it will allow in biotechnology patents. If it allows broad claims, the number and cost of patent interference proceedings in the U.S. and the risk of infringement litigation may increase. If it allows narrow claims, the risk of infringement may decrease, but the value of our rights under our patents, licenses and patent applications may also decrease. Patent applications in which we have rights may never issue as patents, and the claims of any issued patents may not afford meaningful protection for our technologies or products. In addition, patents issued to us or our licensors may be challenged and subsequently narrowed, invalidated or circumvented. Litigation, interference proceedings or other governmental proceedings that we may become involved in with respect to our proprietary technologies or the proprietary technology of others could result in substantial cost to us.

We also rely upon trade secrets, proprietary know-how and continuing technological innovation to remain competitive. Third parties may independently develop such know-how or otherwise obtain access to our technology. While we require our employees, consultants and corporate partners with access to proprietary information to enter into confidentiality agreements, these agreements may not be honored.

Patent litigation is widespread in the biotechnology industry, and any patent litigation could harm our business.

Costly litigation might be necessary to protect a patent position or to determine the scope and validity of third party proprietary rights, and we may not have the required resources to pursue any such litigation or to protect our patent rights. Any adverse outcome in litigation with respect to the infringement or validity of any patents owned by third parties could subject us to significant liabilities to third parties, require disputed rights to be licensed from third parties or require us to cease using a product or technology. With respect to our in-licensed patents, if we attempt to initiate a patent infringement suit against an alleged infringer, it is possible that our applicable licensor will not participate in or assist us with the suit and as a result we may not be able to effectively enforce the applicable patents against the alleged infringers.

We may be unable to obtain or protect our intellectual property rights, and we may be liable for infringing upon the intellectual property rights of others, which may cause us to engage in costly litigation and, if unsuccessful, could cause us to pay substantial damages and prohibit us from selling our products.

At times, we may monitor patent filings for patents that might be relevant to some of our products and product candidates in an effort to guide the design and development of our products to avoid infringement, but may not have conducted an exhaustive search. We may not be able to successfully challenge the validity of third party patents and could be required to pay substantial damages, possibly including treble damages, for past infringement and attorneys' fees if it is ultimately determined that our products infringe such patents. Further, we may be prohibited from selling our products before we obtain a license, which, if available at all, may require us to pay substantial royalties.

Moreover, third parties may challenge the patents that have been issued or licensed to us. We do not believe that PIXUVRI, pacritinib or any of the other compounds we are currently developing infringe upon the rights of any third parties nor are they materially infringed upon by third parties; however, there can be no assurance that our technology

will not be found in the future to infringe upon the rights of others or be infringed upon by others. In such a case, others may assert infringement claims against us, and should we be found to infringe upon their patents, or otherwise impermissibly utilize their intellectual property, we might be forced to pay damages, potentially including treble damages, if we are found to have willfully infringed on such parties' patent rights. In addition to any damages we might have to pay, we may be required to obtain licenses from the holders of this intellectual property, enter into royalty agreements or redesign our compounds so as not to utilize this intellectual property, each of which may prove to be uneconomical or otherwise impossible. Conversely, we may not always be able to successfully pursue our claims against others that infringe upon our technology and the technology exclusively licensed from any third parties. Thus, the proprietary nature of our technology or technology licensed by us may not provide adequate protection against competitors.

Even if infringement claims against us are without merit, or if we challenge the validity of issued patents, lawsuits take significant time, may, even if resolved in our favor, be expensive and divert management attention from other business concerns. Uncertainties resulting from the initiation and continuation of any litigation could limit our ability to continue our operations.

The illegal distribution and sale by third parties of counterfeit versions of a product or stolen product could have a negative impact on our reputation and business.

Third parties might illegally distribute and sell counterfeit or unfit versions of a product, which does not meet our rigorous manufacturing and testing standards. A patient who receives a counterfeit or unfit product may be at risk for a number of dangerous health consequences. Our reputation and business could suffer harm as a result of counterfeit or unfit product sold under our brand name. In addition, thefts of inventory at warehouses, plants or while in-transit, which are not properly stored and which are sold through unauthorized channels, could adversely impact patient safety, our reputation and our business.

We may owe additional amounts for value added tax, or VAT, related to our operations in Europe.

Our European operations are subject to the VAT, which is usually applied to all goods and services purchased and sold throughout Europe. The VAT receivable was \$4.9 million and \$5.5 million as of December 31, 2014 and December 31, 2013, respectively. On April 14, 2009, December 21, 2009 and June 25, 2010, the Italian Tax Authority, or the ITA, issued notices of assessment to our branch, Cell Therapeutics Inc.—Sede Secondaria, or CTI (Europe), based on the ITA's audit of CTI (Europe)'s VAT returns for the years 2003, 2005, 2006 and 2007. The ITA audits concluded that CTI (Europe) did not collect and remit VAT on certain invoices issued to non-Italian clients for services performed by CTI (Europe). The assessments, including interest and penalties, for the years 2003, 2005, 2006 and 2007 are €0.5 million, €5.5 million, €2.5 million and €0.8 million. While we are defending ourselves against the assessments both on procedural grounds and on the merits of the case, there can be no assurances that we will be successful in such defense. Further information pertaining to these cases can be found in Part I, Item 3, Legal Proceedings, and is incorporated by reference herein. If the final decision of the Italian Supreme Court is unfavorable to us, or if, in the interim, the ITA were to make a demand for payment and we were to be unsuccessful in suspending collection efforts, we may be requested to pay to the ITA an amount up to €9.4 million (or approximately \$11.4 million converted using the currency exchange rate as of December 31, 2014) plus collection fees, notification expenses and additional interest for the period lapsed between the date in which the assessments were issued and the date of effective payment.

We are currently subject to certain regulatory and legal proceedings, and may in the future be subject to additional proceedings and/or allegations of wrong-doing, which could harm our financial condition and operating results.

We are currently, and may in the future be, subject to regulatory matters and legal claims, including possible securities, derivative, consumer protection and other types of proceedings pursued by individuals, entities or regulatory bodies. As described in Part I, Item 3, Legal Proceedings, we are currently engaged in a number of pending legal matters. Litigation is subject to inherent uncertainties, and we have had and may in the future have unfavorable rulings and settlements. Adverse outcomes in some or all of such pending cases may result in significant monetary damages or injunctive relief against us. It is possible that our financial condition and operating results could be harmed in any period in which the effect of an unfavorable final outcome becomes probable and reasonably estimable, and if an unfavorable ruling were to occur in any of the legal proceedings we are or may be subject to, our business, financial condition, operating results and prospects could be harmed. We are subject to a variety of claims and lawsuits from time to time, some of which arise in the ordinary course of our business. The ultimate outcome of litigation and other claims is subject to inherent uncertainties, and our view of these matters may change in the future.

Securities class action and shareholder derivative lawsuits are often instituted against issuers. We have been subjected to such actions and we, together with our directors and one former director, presently are subject to a derivative

lawsuit.

We cannot predict with certainty the eventual outcome of pending litigation. In addition, negative publicity resulting from any allegations of wrong-doing could harm our business, regardless of whether the allegations are valid or whether we are liable. Furthermore, we may have to incur substantial time and expense in connection with such lawsuits and management's attention and resources could be diverted from operating our business as we respond to the litigation. Our insurance is subject to high deductibles and there is no guarantee that the insurance will cover any specific claim that we currently face or may face in the future, or that it will be adequate to cover all potential liabilities and damages. In the event of negative publicity resulting from allegations of wrong-doing and/or an adverse outcome under any currently pending or future lawsuit, our business could be materially harmed.

Our net operating losses may not be available to reduce future income tax liability.

We have substantial tax loss carryforwards for U.S. federal income tax purposes, but our ability to use such carryforwards to offset future income or tax liability is limited under section 382 of the Internal Revenue Code of 1986, as amended, as a result of prior changes in the stock ownership of the Company. Moreover, future changes in the ownership of our stock, including those resulting from issuance of shares of our common stock upon exercise of outstanding warrants, may further limit our ability to use our net operating losses.

Due to the fact that we have European branches and subsidiaries conducting operations, together with the fact that we are party to certain contractual arrangements denoting monetary amounts in foreign currencies, we are subject to risk regarding currency exchange rate fluctuations.

We are exposed to risks associated with the translation of euro-denominated financial results and accounts into U.S. dollars for financial reporting purposes. The carrying value of the assets and liabilities, as well as the reported amounts of revenues and expenses, in our European branches and subsidiaries will be affected by fluctuations in the value of the U.S. dollar as compared to the euro. In addition, certain of our contractual arrangements, such as the Servier Agreement, denote monetary amounts in foreign currencies, and consequently, the ultimate financial impact to us from a U.S. dollar perspective is subject to significant uncertainty. Changes in the value of the U.S. dollar as compared to foreign currencies (in particular, the euro) might have an adverse effect on our reported operating results and financial condition.

We may be unable to obtain the raw materials necessary to produce a particular product or product candidate.

We may not be able to purchase the materials necessary to produce a particular product or product candidate in adequate volume and quality. For example, paclitaxel, a material used to produce Opaxio, is derived from certain varieties of yew trees and the supply of paclitaxel is controlled by a limited number of companies. If any raw material required to produce a product or product candidate is insufficient in quantity or quality, if a supplier fails to deliver in a timely fashion or at all or if these relationships terminate, we may not be able to qualify and obtain a sufficient supply from alternate sources on acceptable terms, or at all.

Because there is a risk of product liability associated with our compounds, we face potential difficulties in obtaining insurance, and if product liability lawsuits were to be successfully brought against us, our business may be harmed.

Our business exposes us to potential product liability risks inherent in the testing, manufacturing, marketing and sale of human pharmaceutical products. In particular, as a result of the commercialization of PIXUVRI, our risk with respect to potential product liability has increased. If our insurance covering a compound is not maintained on acceptable terms or at all, we might not have adequate coverage against potential liabilities. Our inability to obtain sufficient insurance coverage at an acceptable cost or otherwise to protect against potential product liability claims could prevent or limit the commercialization of any products we develop. A successful product liability claim could also exceed our insurance coverage and could harm our financial condition and operating results.

We may be subject to claims relating to improper handling, storage or disposal of hazardous materials.

Our research and development activities involve the controlled use of hazardous materials, chemicals and various radioactive compounds. We are subject to federal, state and local laws and regulations, both internationally and domestically, governing the use, manufacture, storage, handlings, treatment, transportation and disposal of such materials and certain waste products and employee safety and health matters. Although we believe that our safety procedures for handling and disposing of such materials comply with applicable law and regulations, the risk of accidental contamination or injury from these materials cannot be eliminated completely. In the event of such an accident, we could be held liable for any damages that result and any such liability not covered by insurance could exceed our resources. Compliance with environmental, safety and health laws and regulations may be expensive, and

current or future environmental regulations may impair our research, development or production efforts.

We depend on sophisticated information technology systems to operate our business and a cyber-attack or other breach of these systems could have a material adverse effect on our business.

We rely on information technology systems to process, transmit and store electronic information in our day-to-day operations. The size and complexity of our information technology systems makes them vulnerable to a cyber-attack, malicious intrusion, breakdown, destruction, loss of data privacy or other significant disruption. Any such successful attacks could result in the theft of intellectual property or other misappropriation of assets, or otherwise compromise our confidential or proprietary information and disrupt our operations. Cyber-attacks are becoming more sophisticated and frequent. We have invested in our systems and the protection of our data to reduce the risk of an intrusion or interruption, and we monitor our systems on an ongoing basis for any current or potential threats. There can be no assurance that these measures and efforts will prevent future interruptions or breakdowns. If we fail to maintain or protect our information technology systems and data integrity effectively or fail to anticipate, plan for or manage significant disruptions to these systems, we could have difficulty preventing, detecting and controlling fraud, have disputes with customers, physicians and other health care professionals, have regulatory sanctions or penalties imposed, have increases in operating expenses, incur expenses or lose revenues or suffer other adverse consequences, any of which could have a material adverse effect on our business, results of operations, financial condition, prospects and cash flows.

Risks Related To the Securities Markets

Shares of our common stock are subordinate to any preferred stock we may issue and to existing and any future indebtedness.

Shares of our common stock rank junior to any shares of our preferred stock that we may issue in the future and to our existing indebtedness, including under our senior secured term loan agreement, and any future indebtedness we may incur, as well as to all creditor claims and other non-equity claims against us and our assets available to satisfy claims on us, including claims in a bankruptcy or similar proceeding. Our senior secured term loan agreement restricts, and any future indebtedness and preferred stock may restrict, payment of dividends on our common stock.

Additionally, unlike indebtedness, where principal and interest customarily are payable on specified due dates, in the case of our common stock, (i) dividends are payable only when and if declared by our Board of Directors or a duly authorized committee of our Board of Directors and (ii) as a corporation, we are restricted to making dividend payments and redemption payments out of legally available assets. We have never paid a dividend on our common stock and have no current intention to pay dividends in the future. Furthermore, our common stock places no restrictions on our business or operations or on our ability to incur indebtedness or engage in any transactions, subject only to the voting rights available to our shareholders generally.

We may not be able to maintain our listings on The NASDAQ Capital Market and the MTA in Italy, or trading on these exchanges may otherwise be halted or suspended, which may make it more difficult for investors to sell shares of our common stock and consequently may negatively impact the price of our common stock.

Maintaining the listing of our common stock on The NASDAQ Capital Market requires that we comply with certain listing requirements. We have in the past and may in the future fail to continue to meet one or more listing requirements. For example, in June 2012, we received a notification from The NASDAQ Stock Market indicating non-compliance with the requirement to maintain a minimum closing bid price of \$1.00 per share and that we would be delisted if we did not timely regain compliance. We regained compliance through a reverse stock split in September 2012, but we could fail to meet the continued listing requirements as a result of a decrease in our stock price or otherwise.

If our common stock ceases to be listed for trading on The NASDAQ Capital Market for any reason, it may harm our stock price, increase the volatility of our stock price, decrease the level of trading activity and make it more difficult

for investors to buy or sell shares of our common stock. Our failure to maintain a listing on The NASDAQ Capital Market may constitute an event of default under our senior secured term loan and any future indebtedness, which would accelerate the maturity date of such debt or trigger other obligations. In addition, certain institutional investors that are not permitted to own securities of non-listed companies may be required to sell their shares adversely affecting the market price of our common stock. If we are not listed on The NASDAQ Capital Market or if our public float falls below \$75 million, we will be limited in our ability to file new shelf registration statements on SEC Form S-3 and/or to fully use one or more registration statements on SEC Form S-3. We have relied significantly on shelf registration statements on SEC Form S-3 for most of our financings in recent years, so any such limitations may harm our ability to raise the capital we need. Delisting from The NASDAQ Capital Market could also affect our ability to maintain our listing or trading on the MTA in Italy. Trading in our common stock has been halted or suspended on both The NASDAQ Capital Market and MTA in the past and may also be halted or suspended in the future due to market or trading conditions at the discretion of The NASDAQ Stock Market, CONSOB or the Borsa Italiana (which ensures the development of the managed markets in Italy). Any halt or suspension in the trading in our common stock may negatively impact the market price of our common stock.

The market price of shares of our common stock is extremely volatile, which may affect our ability to raise capital in the future and may subject the value of your investment in our securities to sudden decreases.

The market price for securities of biopharmaceutical and biotechnology companies, including ours, historically has been highly volatile, and the market from time to time has experienced significant price and volume fluctuations that are unrelated to the operating performance of such companies. For example, during the 12-month period ended March 5, 2015, our stock price has ranged from a low of \$2.00 to a high of \$4.22. Fluctuations in the market price or liquidity of our common stock may harm the value of your investment in our common stock.

Factors that may have an impact, which, depending on the circumstances, could be significant, on the market price and marketability of our securities include:

- announcements by us or others of results of clinical trials and regulatory actions;
- announcements by us or others of serious adverse events that have occurred during administration of our products to patients;
- announcements by us or others relating to our ongoing development and commercialization activities;
- announcements of technological innovations or new commercial therapeutic products by us, our collaborative partners or our present or potential competitors;
- our issuance of debt or equity securities, which we expect to pursue to generate additional funds to operate our business, or any perception from time to time that we will issue such securities;
- our quarterly operating results;
- liquidity, cash position or financing needs;
- developments or disputes concerning patent or other proprietary rights;
- developments in relationships with collaborative partners;
- acquisitions or divestitures;
- our ability to realize the anticipated benefits of our compounds;
- litigation and government proceedings;
- adverse legislation, including changes in governmental regulation;
- third party reimbursement policies;
- changes in securities analysts' recommendations;
- short selling of our securities;
- changes in health care policies and practices;
- a failure to achieve previously announced goals and objectives as or when projected;
- halting or suspension of trading in our common stock on The NASDAQ Capital Market or on the MTA; and
- general economic and market conditions.

Anti-takeover provisions in our charter documents, in our shareholder rights agreement, or rights plan, under Washington law and in other applicable instruments could make removal of incumbent management or an acquisition of us, which may be beneficial to our shareholders, more difficult.

Provisions of our articles of incorporation and bylaws may have the effect of deterring or delaying attempts by our shareholders to remove or replace management, to commence proxy contests, or to effect changes in control. These provisions include:

- elimination of cumulative voting in the election of directors;
- procedures for advance notification of shareholder nominations and proposals;
- the ability of our Board of Directors to amend our bylaws without shareholder approval; and
- the ability of our Board of Directors to issue shares of preferred stock without shareholder approval upon the terms and conditions and with the rights, privileges and preferences as our Board of Directors may determine.

Pursuant to our rights plan, an acquisition of 20 percent or more of our common stock by a person or group, subject to certain exceptions, could result in the exercisability of the preferred stock purchase right accompanying each share of our common stock (except those held by a 20 percent shareholder, which become null and void), thereby entitling the holder to receive upon exercise, in lieu of a number of units of preferred stock, that number of shares of our common stock having a market value of two times the exercise price of the right. The existence of our rights plan could have the effect of delaying, deterring or preventing a third party from making an acquisition proposal for us and may inhibit a change in control that some, or a majority, of our shareholders might believe to be in their best interest or that could give our shareholders the opportunity to realize a premium over the then-prevailing market prices for their shares.

In addition, as a Washington corporation, we are subject to Washington's anti-takeover statute, which imposes restrictions on some transactions between a corporation and certain significant shareholders. Other existing provisions applicable to us that could have an anti-takeover effect include our executive employment agreements and certain provisions of our outstanding equity-based compensatory awards that allow for accelera