AVEO PHARMACEUTICALS INC
Form 10-K
March 13, 2014
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UNITED STATES

SECURITIES AND EXCHANGE COMMISSION

Washington, D.C. 20549

FORM 10-K

(Mark One)

x **ANNUAL REPORT PURSUANT TO SECTION 13 OR 15(d) OF THE SECURITIES EXCHANGE ACT OF 1934**
For the fiscal year ended: December 31, 2013

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: 001-34655

AVEO PHARMACEUTICALS, INC.

(Exact Name of Registrant as Specified in Its Charter)

Delaware	04-3581650
(State or Other Jurisdiction of Incorporation or Organization)	(I.R.S. Employer Identification No.)

650 East Kendall Street

Cambridge, Massachusetts 02142

(Address of Principal Executive Offices) (zip code)

Registrant s telephone number, including area code: (617) 299-5000

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

Title of each class	Name of each exchange on which registered
Common Stock, $.001 par value	NASDAQ Global Market

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

None

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

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

Indicate by check mark whether the registrant (1) has filed all reports required to be filed by Section 13 or 15(d) of the Securities Exchange Act of 1934 during the 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 x No ¨

Indicate by check mark whether the registrant has submitted electronically and posted on its corporate Web site, if any, every Interactive Data File required to be submitted and posted pursuant to Rule 405 of Regulation S-T (§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 x No ¨

Indicate by check mark if disclosure of delinquent filers pursuant to Item 405 of Regulation S-K (§229.405) is not contained herein, and will not be contained, to the best of registrant s knowledge, in definitive proxy or information statements incorporated by reference in Part III of this Form 10-K or any amendment to this Form 10-K. ¨

Indicate by check mark whether the registrant is a large accelerated filer, an accelerated filer, a non-accelerated filer, or a smaller reporting company. See 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	x
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 Exchange Act). Yes ¨ No x

The aggregate market value of the registrant s common stock, $0.001 par value per share (Common Stock), held by non-affiliates of the registrant, based on the last reported sale price of the Common Stock on the NASDAQ Global Market at the close of business on June 28, 2013, was $93,057,173.

The number of shares outstanding of the registrant s Common Stock as of February 28, 2014: 51,793,605

Documents incorporated by reference:

Portions of our definitive proxy statement for our 2014 annual meeting of stockholders are incorporated by reference into Part III of this Annual Report on Form 10-K.

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References to AVEO

Throughout this Form 10-K, the words we, us, our and AVEO , except where the context requires otherwise, refer to AVEO Pharmaceuticals, Inc. and its consolidated subsidiaries, and our board of directors refers to the board of directors of AVEO Pharmaceuticals, Inc.

Forward-Looking Information

This report contains forward-looking statements regarding, among other things, our future discovery and development efforts, our collaborations, our future operating results and financial position, our business strategy, and other objectives for our operations. You can identify these forward-looking statements by their use of words such as anticipate, believe, estimate, expect, forecast, intend, plan, project, and other words and terms of similar meaning. You also can identify them by the fact that they do not relate strictly to historical or current facts. There are a number of important risks and uncertainties that could cause our actual results to differ materially from those indicated by forward-looking statements. These risks and uncertainties include those inherent in pharmaceutical research and development, such as adverse results in our drug discovery, preclinical trials and clinical development activities, our ability to obtain any necessary financing to conduct our planned activities, decisions made by the U.S. Food and Drug Administration and other regulatory authorities with respect to the development and commercialization of our drug candidates, our ability to obtain, maintain and enforce intellectual property rights for our drug candidates, our dependence on our existing and future strategic partners, and other risk factors. Please refer to the section entitled Risk Factors in Part I Item 1A of this report for a description of these risks and uncertainties. Unless required by law, we do not undertake any obligation to publicly update any forward-looking statements.

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PART I

ITEM 1. Business

Overview

We are a biopharmaceutical company committed to discovering and developing targeted therapies designed to provide substantial impact in the lives of people with cancer by addressing unmet medical needs. AVEO s proprietary Human Response Platform provides the company unique insights into cancer and related disease biology and is being leveraged in the discovery and clinical development of its therapeutic candidates. Some of the programs we are developing include:

AV-203: AV-203 is an anti-ErbB3 monoclonal antibody with broad therapeutic potential. AV-203 has high ErbB3 affinity and potent anti-tumor activity in mouse models. AV-203 inhibits the activity of the ErbB3 receptor and our preclinical studies suggest that neuregulin-1, or NRG1, levels predict AV-203 anti-tumor activity in preclinical models. We have completed a phase 1 dose escalation study of AV-203 showing no dose limiting toxicities at maximum dose of 20mg/kg. The single-agent expansion cohort of this study among patients with a specific biomarker has been discontinued. We are currently partnered with Biogen Idec with respect to AV-203, and Biogen Idec has an option for development outside of the United States. Subject to our ability to regain certain rights from Biogen Idec with respect to AV-203, we will seek to resume clinical development with a third party.

Ficlatuzumab: Ficlatuzumab is a Hepatocyte Growth Factor, or HGF, inhibitory antibody. HGF is the sole known ligand of the c-Met receptor which is believed to trigger many activities that are involved in cancer development and metastasis. We have completed two phase 1 clinical studies and a phase 2 clinical study evaluating ficlatuzumab in combination with gefitinib in first line non-small cell lung cancer, or NSCLC. The phase 2 trial failed to demonstrate a statistically significant benefit in the intent- to-treat population. However, an exploratory analysis using a serum-based molecular diagnostic test identified a patient sub-population that experienced a progression free survival and overall survival benefit on the combination therapy in the phase 2 trial. We are currently seeking a partner that could support further clinical development in this patient population.

Tivozanib. In 2006, we acquired exclusive rights to develop and commercialize tivozanib, worldwide outside of Asia pursuant to a license agreement we entered into with Kirin Brewery Co. Ltd. (now Kyowa Hakko Kirin), or KHK. Tivozanib is an investigational tyrosine kinase inhibitor of all three vascular endothelial growth factor, or VEGF receptors. As discussed below under the heading Strategic Partnerships, we entered into a strategic collaboration with Astellas in which we agreed to share responsibility with Astellas for the continued development and commercialization of tivozanib in the United States, Mexico and Canada, which we refer to collectively as North America, and Europe. Throughout the rest of the world, outside of North America, Europe and Asia, we granted Astellas an exclusive, royalty-bearing license to develop and commercialize tivozanib. On June 10, 2013, we received a complete response letter from the U.S. Food and Drug Administration, or FDA, informing us that the FDA will not approve in its present form our New Drug Application, or NDA, for tivozanib for the treatment of patients with advanced renal cell carcinoma, or RCC. In February 2014, Astellas informed us of its intent to end our collaboration for tivozanib. Currently, our focus with tivozanib is to wind down our activities related to our partnership with Astellas, including on-going support for patients who continue to receive treatment with tivozanib related to our clinical trials in RCC, breast cancer and colorectal cancer, which we had previously announced that we were discontinuing prior to Astellas exercise of its termination. In August 2014, pursuant to the terms of the license agreement, in connection with the termination, all rights for the development and commercialization of tivozanib will revert to AVEO. We will consider further partnering options based on what we believe is a favorable risk and benefit profile which could provide benefit to patients in certain indications.

AV-380 Program: In 2012, we initiated a program focusing on cachexia, a serious and common complication of advanced cancer and a number of chronic diseases that is characterized by unintentional

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weight loss, progressive muscle wasting, and a loss of appetite. Our primary research focus is in the area of cancer cachexia where there is a major unmet need. Over 400,000 patients in the United States being treated for cancer also suffer from cachexia. In addition, cachexia is also associated with diseases outside of cancer including congestive heart failure, chronic kidney disease, and chronic obstructive pulmonary disease. AV-380, our lead drug candidate, is a potent humanized IgG1 inhibitory monoclonal antibody targeting growth differentiating factor-15, or GDF-15, a divergent member of the TGF-b. family. In connection with this program, we have in-licensed certain patents and patent applications from St. Vincent s Hospital in Sydney, Australia.

We believe that AV-380 represents a unique approach to treating cachexia because it addresses key underlying mechanisms of the syndrome. In preclinical models, AV-380 has been shown to increase food intake, reverse body weight loss and restore normal body composition. Appropriate IND-enabling efforts, including cell line development, have been initiated to prepare AV-380 for future clinical development, and we expect that we will begin a phase 1 clinical study of AV-380 in cachexia in the second half of 2015. We plan to evaluate opportunities for partnerships to expand the development of AV-380 in cachexia associated with non-cancer indications including chronic heart failure, chronic kidney disease and chronic obstructive pulmonary disease to leverage the full potential of this asset.

Going forward, we plan to focus our internal resources to advance potential first-in-class opportunities, such as our AV-380 program. We also plan to utilize external resources through innovative collaborations and strategic partnerships to develop our other assets. We plan to evaluate our potential drug candidates in accordance with the following criteria:

Identify diseases where no other therapies exist or where there is a well-defined patient population with clear unmet medical needs;

Provide a clear path to proof of concept and approval with reasonable probabilities of success; and

Pursue programs that can deliver value inflections within a projected framework.

Product Pipeline

AV-203: Anti-ErbB3 Antibody

Through the use of our Human Response Platform, our scientists have highlighted the importance of the ErbB3 receptor in tumor growth. ErbB3 belongs to a family of four proteins that also includes epidermal growth factor receptor, or EGFR, and HER2, both of which have been implicated in promoting the growth of significant numbers of tumors, particularly in breast and lung cancers.

ErbB3 is believed to be an important receptor regulating cancer cell growth and survival, and high ErbB3 levels have been shown to correlate with poor prognoses in several tumor types. It has also been implicated in resistance to certain drugs which target EGFR in lung cancer and with resistance to radiotherapy. In addition, while the anti-HER2 antibody Herceptin has been very successful in treating many breast tumors that express HER2, HER2 is only overexpressed (HER2 positive) in roughly 25% of breast cancer and as many as 60% of HER2 positive patients do not respond to treatment, as reported in a 2007 Herceptin review by C.A. Hudis published in *The New England Journal of Medicine*. Because ErbB3 preferentially binds with HER2, we believe that breast cancer patients who do not respond well to anti-HER2 therapy might benefit from drug combinations with an anti-ErbB3 antibody. AV-203 inhibits the activity of the ErbB3 receptor and our preclinical studies suggest that neuregulin-1, or NRG1, levels predict AV-203 anti-tumor activity.

In March 2009, we entered into an exclusive option and license agreement with Biogen Idec, under which we granted Biogen Idec an exclusive option to obtain rights to co-develop (with us) and commercialize our ErbB3-targeted antibodies for the potential treatment and diagnosis of cancer and other diseases outside of North

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America. Under the agreement, we are responsible for developing ErbB3 antibodies through completion of the first phase 2 clinical trial designed in a manner that, if successful, will generate data sufficient to support advancement to a phase 3 clinical trial.

Within a specified time period after we complete the phase 2 clinical trial and deliver to Biogen Idec a detailed data package containing the results thereof, Biogen Idec may elect to obtain (1) a co-exclusive (with us) worldwide license under our relevant intellectual property to develop and manufacture ErbB3 antibody products, and (2) an exclusive license under our relevant intellectual property to commercialize ErbB3 antibody products in all countries in the world other than in North America. We retain the exclusive right to commercialize ErbB3 antibody products in North America. Until completion of the first phase 2 clinical trial, we are solely responsible for the research, development, and manufacturing of ErbB3 antibody(ies) pursuant to a written work plan meeting specific pre-agreed guidelines. We are solely responsible for all expenses incurred through completion of the first phase 2 clinical trial. If Biogen Idec exercises its option to obtain exclusive commercialization rights to ErbB3 products in its territory, then we will be solely responsible, subject to a mutually agreed development plan, budget and the oversight of a joint development committee, for the global development of ErbB3 antibody products, except that Biogen Idec will be solely responsible for ErbB3 antibody product development activities that relate solely to the Biogen Idec territory. We and Biogen Idec will share global development costs (including manufacturing costs to support development) for ErbB3 antibody products equally, except that Biogen Idec will be solely responsible for all development costs associated solely with the development of ErbB3 antibody products for its territory, and we will be solely responsible for all development costs associated solely with the development of ErbB3 antibody products for North America. We are currently seeking to regain certain rights from Biogen Idec, which will allow for the potential for future clinical development with a third party.

Ficlatuzumab: Hepatocyte Growth Factor (HGF) Inhibitory Antibody

Through the use of our Human Response Platform, our scientists have identified the HGF/c-Met pathway as a significant driver of tumor growth. HGF is a protein that circulates in the blood and binds to and activates a receptor called c-Met. HGF is the sole known ligand of c-Met receptor, which is believed to trigger many activities that are involved in cancer development and metastasis. Altered HGF/c-Met signaling is observed in many tumors including lung, head and neck, gastric, bladder, breast, ovarian, prostate and colorectal cancers, certain sarcomas and in multiple myeloma and leukemias. There are no approved therapies that specifically target the HGF/c-Met pathway.

In September 2012, we presented results of the phase 2 portion of a phase 1b/2 clinical trial, which we refer to as the ficlatuzumab phase 2 trial, testing a combination of ficlatuzumab with gefitinib, an epidermal growth factor receptor, or EGFR, tyrosine kinase inhibitor, randomized 1:1 versus gefitinib alone in patients with previously untreated locally advanced or metastatic non-small cell lung cancer, or NSCLC. Patients who demonstrated disease progression during treatment with gefitinib alone had the opportunity to be treated with ficlatuzumab in combination with gefitinib provided that safety was maintained and the patient continued to meet trial eligibility criteria. This 188-patient, randomized clinical trial, which was conducted in Asia, studied response rate and progression-free survival, or PFS, in distinct patient subsets: those with activating EGFR mutations and those with wild-type EGFR. In addition, we are evaluating patient outcome based on c-Met levels expressed in their tumors. The primary endpoint of the study was overall response rate, referred to as ORR; secondary endpoints included PFS, overall survival, or OS, and correlation of biomarkers with clinical activity. In the intent to treat, referred to as ITT, population, the addition of ficlatuzumab to gefitinib did not result in statistically significant improved ORR or PFS in Asian treatment-naïve NSCLC patients. The OS hazard ratio in the ITT population for ficlatuzumab plus gefitinib versus gefitinib monotherapy was 0.98 (95% CI 0.66, 1.46). The combination was well-tolerated, with no clinically meaningful differences in adverse event rates observed between the two arms.

An exploratory analysis using a serum-based molecular diagnostic test identified a patient sub-population that experienced a progression free survival and overall survival benefit on the combination therapy in the

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ficlatuzumab phase 2 trial. These results will be presented at an upcoming scientific meeting. We believe that these results support the continued clinical evaluation of ficlatuzumab in NSCLC and we are currently exploring potential partnership opportunities to support further clinical research of ficlatuzumab.

In November 2011, we entered into an agreement with Boehringer Ingelheim International GmbH, or Boehringer Ingelheim, for large-scale process development and clinical manufacturing of ficlatuzumab. In connection with the agreement, Boehringer Ingelheim is producing ficlatuzumab at its biopharmaceutical sites in Fremont, CA (drug substance) and Beberach, Germany (drug product). We have retained all rights to the development and commercialization of ficlatuzumab.

Tivozanib: Inhibitor of VEGF Receptors 1, 2 & 3

Tivozanib is a potent, selective long half-life inhibitor of all three VEGF receptors that is designed to optimize VEGF blockade while minimizing off-target toxicities. The demonstrated clinical results with tivozanib are supported by its core biochemical properties of potency, selectivity and long half-life inhibition of all three VEGF receptors. The potency of tivozanib across VEGF receptors 1, 2 and 3 provides a comprehensive blockade of the VEGF pathway. Its high level of selectivity for all three VEGF receptors is designed to minimize unintended side effects, such as fatigue, diarrhea and hand-foot syndrome, which are often associated with the currently approved therapies. Hypertension and dysphonia were the most commonly reported side effects in patients treated with tivozanib. The occurrence of hypertension and dysphonia are driven by inhibition of the VEGF pathway, and suggest that the pathway has been substantially inhibited by tivozanib. Both hypertension and dysphonia were manageable and reversible in clinical trials. In addition, because tivozanib has demonstrated a long half-life, meaning the time it takes for the concentration of a drug in circulation to be reduced by one-half, we believe it maintains a more consistent blockade of the relevant receptors.

We entered into a collaboration and license agreement with Astellas in February 2011, pursuant to which we and Astellas shared responsibility for tivozanib, including expenses for continued development and any future commercialization of tivozanib, in North America and Europe. Astellas was responsible for continued development and any future commercialization of tivozanib outside of North America, Europe and Asia. Upon entering into our license agreement with KHK, we made a cash payment in the amount of $5.0 million to KHK. In the first quarter of 2010, we paid KHK a $10.0 million milestone payment in connection with the initiation of our phase 3 clinical trial of tivozanib for the treatment of patients with advanced RCC. In the first quarter of 2011, we paid KHK $22.5 million related to the up-front license payment received under the collaboration and license agreement with Astellas. In December 2012, we made a $12.0 million milestone payment to KHK in connection with the acceptance of our NDA filing for tivozanib for the treatment of patients with advanced RCC.

In 2012, we announced detailed data from our global, phase 3 clinical trial comparing the efficacy and safety of tivozanib with Nexavar® (sorafenib), an approved therapy, for first-line treatment in advanced RCC, which we refer to as the TIVO-1 (Tivozanib Versus Sorafenib in 1st line Advanced RCC) study. The TIVO-1 study was conducted in patients with advanced clear cell RCC who had undergone a prior nephrectomy (kidney removal) and who had not received any prior VEGF- or mTOR-targeted therapy. In this trial, we measured, among other things, each patient s progression-free survival, or PFS, which refers to the period of time that began when a patient entered the clinical trial and ended when either the patient died or the patient s cancer had grown by a specified percentage or spread to a new location in the body. This phase 3 trial met its primary endpoint for progression-free survival.

In June 2013, we received a Complete Response letter from the FDA informing us that the FDA would not approve the NDA for tivozanib for the treatment of patients with advanced RCC. In view of the FDA s decision, and our subsequent decision not to pursue tivozanib development in RCC, we announced a strategic restructuring to refocus our efforts on the on-going clinical development of tivozanib in colorectal and breast cancer and on the advancement of key pipeline and preclinical assets. We evaluated tivozanib in additional clinical programs including our BATON (Biomarker Assessment of Tivozanib in ONcology) program, assessing biomarkers in solid tumors that may be predictive of clinical response to tivozanib in patients with metastatic colorectal cancer, and other clinical trials assessing locally recurrent or metastatic triple negative breast cancer.

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The BATON study in patients with colorectal cancer, led by Astellas, was an open-label, randomized Phase 2 study with a primary endpoint evaluating the superiority of tivozanib in combination with modified FOLFOX6, a standard chemotherapy, compared to bevacizumab in combination with modified FOLFOX6 as first-line treatment in patients with advanced metastatic colorectal cancer. On December 13, 2013, we announced that the study was unlikely to meet the primary endpoint in the intent-to-treat population and on February 14, 2014, we announced that we and Astellas agreed to discontinue this study.

The BATON breast cancer study initiated patient enrollment in December 2012 in a randomized, double-blind, multicenter Phase 2 clinical trial, evaluating the efficacy of tivozanib in combination with paclitaxel compared to placebo in combination with paclitaxel in patients with locally recurrent or metastatic triple negative breast cancer who have received no more than one systemic therapy for advanced or metastatic breast cancer. On January 30, 2014, we announced that we and Astellas jointly decided to discontinue the BATON breast cancer clinical trial, due to insufficient enrollment.

On February 12, 2014, Astellas elected to exercise its right to terminate our collaboration and license agreement as a result of the limited scope of development for tivozanib moving forward. This termination will be effective August 2014, at which time all rights for the development and commercialization of tivozanib will revert to AVEO. We will consider further partnering options based on what we believe is a favorable risk and benefit profile which could provide benefit to patients in certain indications.

AV-380 Program in Cachexia

In 2012, we initiated a program focusing on cachexia, which we now refer to as our AV-380 program. Cachexia is a serious and common complication of advanced cancer and a number of chronic diseases. It is defined as a multi-factorial syndrome of involuntary weight loss characterized by an ongoing loss of skeletal muscle mass (with or without loss of fat mass) that cannot be fully reversed by conventional nutritional support and leads to progressive functional impairment. The pathophysiology is characterized by a negative protein and energy balance driven by a variable combination of reduced food intake and abnormal metabolism. Other symptoms or conditions associated with cachexia include anemia, breathing difficulties, edema, insulin resistance, muscle weakness/asthenia, and fatigue.

In connection with our cachexia program, we have in-licensed certain patents and patent applications from St. Vincent s Hospital in Sydney, Australia. In December 2013, we presented preclinical data at the 7th Annual Cachexia Conference in Kobe, Japan, demonstrating that growth differentiating factor-15, or GDF-15, induces anorexia and cachexia in mice, suggesting GDF-15 to be a novel target for cachexia. In 2013, we initiated cell line development of AV-380, an antibody discovered using our Human Response Platform, and nominated AV-380 as the development candidate for the program. Appropriate IND-enabling efforts, including cell line development, have been initiated to prepare AV-380 for future clinical development. We expect to initiate clinical development of AV-380 in the second half of 2015.

We believe that cachexia represents a significant area of patient need, particularly in cancer. Weight loss during cancer treatment is associated with more chemotherapy-related side effects fewer completed cycles of chemotherapy, a reduction in response to therapy and decreased survival rates (*J Gastroenterol* 2013; *Eur J Cancer* 1998; *Br J Cancer* 2004). In a cohort of over 3,000 patients in the U.S. studied by the Eastern Cooperative Oncology Group, or ECOG, the prevalence of weight loss even before starting chemotherapy was observed to be substantial across several cancers: over 80% in pancreatic and gastric cancers and over 50% in prostate, colorectal and lung cancers (*Am Med Journal* 1980). It is estimated that more than 30% of all cancer patients die due to cachexia and over half of cancer patients who die do so with cachexia present. (*J Cachexia Sarcopenia Muscle* 2010). In the United States, the estimated prevalence of cancer cachexia is over 400,000 patients (*Am J Clin Nutr* 2006).

There are currently few effective treatment options for cachexia. Cancer cachexia is diagnosed and treated according to four categories: anorexia and food intake, catabolic drive (the breakdown of molecules into smaller

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units to release energy), muscle mass and strength, and function and psychosocial effect. Treatments attempt to address or reverse contributory factors for each category. Only megesterol acetate and medroxyprogesterone are approved to treat cachexia, each exclusively in Europe, despite only about 30% of treated patients showing improvements in appetite and weight gain, which are short term and not accompanied by improvement in quality of life or survival (*Curr Opin Oncol.* 2006). As such, we believe that an effective treatment for cachexia could potentially improve patient outcomes and address a major medical need in patients with cancer as well as other chronic diseases, such as obstructive lung disease, heart failure and kidney disease where, in total, millions of patients suffer from cachexia associated with these chronic diseases. (*Am J Clin Nutr* 2006).

Other Pipeline Programs

Using our Human Response Platform, we have identified a number of other promising targets that appear to be potent drivers of tumor growth. Genetic screens conducted using the Human Response Platform have demonstrated that activation of the Notch signaling pathway plays an important role in tumor formation and the maintenance of cancer stem cell populations in tumors. Our team has demonstrated inhibition of tumor growth with a Notch 1 antibody candidate in preclinical tumor models. Work in our Human Response Platform has also identified Fibroblast Growth Factor ligands and receptors as powerful drivers of tumor growth in a variety of tumor models and implicated the activation of the pathway in tumor development.

Our Human Response Platform

We were founded with the goal of developing a fundamentally new kind of pre-clinical cancer model designed to overcome many of the limitations of traditional xenograft models, and thereby improve the probability of success in developing new cancer drugs. We utilize these novel models to identify and validate target genes which drive tumor growth, to identify drugs which can block the function of these targets, and to identify patients who are most likely to respond favorably to treatment with such drugs. We have used these models to advance drugs in our pipeline and in collaboration with our strategic partners such as Merck & Co., Inc., or Merck, OSI Pharmaceuticals, Inc., or OSI, Astellas and Biogen Idec. Our cancer models, together with the various techniques we have developed to use these models to aid in the discovery and development of new cancer drugs, are collectively referred to as our Human Response Platform. Key components of our Human Response Platform are covered by issued patents or pending patent applications. We believe that our platform provides unique insights into cancer biology that may provide us and our strategic partners with a competitive advantage in all phases of cancer drug discovery and development.

We believe that our novel cancer models have a number of unique advantages over traditional xenografts and other methods of developing cancer models used in many academic settings. First, because the tumors grow naturally in the subject animals, the normal interactions between tumors and the tissues around them, including blood vessels, are preserved. This is not the case in traditional xenografts, where human tumor cells are implanted into mice, and certain of the important cellular signals sent by the growing human tumor may not be recognized by the surrounding mouse cells. Second, as is the case in human cancer, the cancer cells grow alongside normal cells, whereas in many other cancer models, all of the cells of the subject animal contain the cancer-causing mutations. Third, because of the switch that we introduce into our models, we can activate the cancer-causing mutations after the subject animals are born, replicating what is seen in many human cancers. In many other models, these mutations are activated before the subject animals are born, and interfere with their normal embryonic development. Finally, because tumors in our model develop spontaneously after introduction of the initial cancer causing mutations, we can develop populations of tumors that exhibit differences in genetic backgrounds, again much more akin to what is seen in a population of human tumors.

Because each of the tumors that develop in our models accumulates random genetic mutations independently, populations of tumors in our models exhibit a significant degree of genetic heterogeneity. Consequently, the tumors that develop in our models, like human tumor populations, typically exhibit variation in response to anti-cancer drugs. The tumors in our models have been studied extensively for genetic characteristics, providing an opportunity

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to correlate the genetic makeup, or genetic context, of each tumor with its relative sensitivity or resistance to a given anti-cancer drug. By understanding the genetic context of tumors that respond to particular drugs, we hope to identify genetic markers, or biomarkers, that can be measured in patients prior to treatment to select or predict which tumors, tumor subtypes, or patient subsets are most likely to respond to a given anti-cancer drug. We are using this approach to identify potential biomarkers for our pipeline drugs and it will be important to demonstrate that the biomarkers we identify translate into clinical benefit in humans.

Efforts to identify predictive biomarkers for our development programs are also ongoing.

Competition

The biotechnology and pharmaceutical industries are highly competitive. There are many pharmaceutical companies, biotechnology companies, public and private universities and research organizations actively engaged in the research and development of products that may be similar to our products. A number of multinational pharmaceutical companies, as well as large biotechnology companies, including Roche Laboratories, Inc., or Roche, Pfizer Inc., or Pfizer, Bayer HealthCare AG, or Bayer, Sanofi-Aventis, US, LLC, Amgen, Inc. and GlaxoSmithKline plc, or GSK, are pursuing the development or are currently marketing pharmaceuticals that target VEGF, HGF and ErbB3, or other oncology pathways on which we are focusing. It is probable that the number of companies seeking to develop products and therapies for the treatment of unmet needs in the lives of people with cancer will increase.

Many of our competitors, either alone or with their strategic partners, have greater financial, technical and human resources than we do and greater experience in the discovery and development of product candidates, obtaining FDA and other regulatory approvals of products and the commercialization of those products. Accordingly, our competitors may be more successful than we may be in obtaining approval for drugs and achieving widespread market acceptance. Our competitors drugs may be safer and more effective, or more effectively marketed and sold, than any drug we may commercialize and may render our product candidates obsolete or non-competitive before we can recover the expenses of developing and commercializing any of our product candidates. We anticipate that we will face intense and increasing competition as new drugs enter the market and advanced technologies become available.

AV-203 Program Competition

We believe the most direct competitors to our AV-203 program that are in phase 1 and phase 2 development are monoclonal antibodies that specifically target the ErbB3 receptor, including Merrimack Pharmaceuticals, Inc. s and Sanofi-Aventis US LLC s MM-121, which is currently in phase 2 clinical development, and Daiichi Sankyo, Inc. s and Amgen, Inc. s patritumab (AMG-888), which is also in phase 2 clinical development. Other clinical-stage ErbB3-specific competitors include Roche s RG-7116, Novartis s LJM716, Regeneron s REGN1400, GSK s GSK-2849330 and Kolltan s KTN-3379. Clinical stage competitor s targeting ErbB3 in addition to other targets include Roche s MEHD7945A, and Merrimack Pharmaceuticals, Inc. s MM-111 and MM-141.

Ficlatuzumab Competition

We believe the products that are considered competitive with ficlatuzumab include those agents targeting the HGF/c-Met pathway. The agents exclusively targeting this pathway consist of the only other HGF-targeted antibody, Amgen s AMG-102 (rilotumumab), currently in a phase 3 clinical trial, as well as Lilly s c-Met receptor antibody LY-2875358, currently in multiple phase 2 trials. In addition, Roche is developing a c-Met receptor antibody onartuzumab (MetMAb/ 5D5 Fab), which is in multiple phase 3 trials. Roche recently announced that an independent data monitoring committee recommended that its phase 3 trial of onartuzumab in second and third line NSCLC be stopped due to lack of efficacy.

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Other marketed or late clinical-stage drugs which target the HGF/c-Met pathway, though not exclusively, include Pfizer s PF-2341066 (Xalkori, crizotinib), Exelixis Inc. s XL-184 (Cometriq, cabozantinib), ArQule, Inc. s/ Daiichi Sankyo, Inc. s ARQ-197 (tivantanib), Mirati Therapeutics (formerly MethylGene) MGCD-265, Eisai Co. Ltd. s E-7050 (golvatinib), Exelixis Inc. s and GSK s XL-880 (foretinib), Incyte Corp. s and Novartis s INCB-028060 and Sanofi-Aventis s SAR-125844, EMD Serono s MSC2156119J, Amgen Astellas BioPharma s AMG 337, and Bristol-Myers Squibb Company s and Aslan Pharmaceuticals BMS-777607.

Tivozanib Competition

There are currently nine FDA-approved drugs in oncology which target the VEGF pathway. Seven of the FDA-approved VEGF pathway inhibitors are oral small molecule receptor tyrosine kinase inhibitors, or TKIs. Nexavar (sorafenib) and Stivarga (regorafenib) are marketed by Bayer and Onyx, a subsidiary of Amgen, Sutent (sunitinib) and Inlyta (axitinib) are marketed by Pfizer, and Votrient (pazopanib) is marketed by GSK. Most of these approved VEGFR TKIs are not specific to the VEGF receptors. Nexavar is approved for advanced RCC and unresectable hepatocellular cancer. Stivarga is approved for refractory metastatic colorectal cancer, or mCRC, and refractory gastrointestinal stromal tumors, or GIST. Sutent is approved for advanced RCC, GIST, and progressive, well-differentiated pancreatic neuroendocrine tumors. Inlyta is approved for advanced RCC after failure of one prior systemic therapy. Votrient is approved for advanced RCC and advanced soft tissue sarcoma after prior chemotherapy. Caprelsa (vandetanib), marketed by AstraZeneca, and Cometriq (cabozantinib), marketed by Exelixis, are approved for medullary thyroid carcinoma.

Avastin (bevacizumab), marketed by Roche/Genentech, is an infused monoclonal antibody approved in combination with other anti-cancer agents for the treatment of mCRC, non-squamous non-small cell lung cancer, and metastatic RCC. It is also approved as a monotherapy for the treatment of glioblastoma in patients with progressive disease following prior therapy. Zaltrap (zif-aflibercept), marketed by Sanofi and Regeneron, is a VEGF-trap molecule that binds to multiple circulating VEGF factors, and is approved in combination with standard chemotherapy agents for treatment of second line mestatatic CRC.

Many of the approved VEGF pathway inhibitor agents are in ongoing development in additional cancer indications. Additionally, we are aware of a number of companies that have ongoing phase 2 and 3 programs to develop both small molecules and biologics that target the VEGF pathway.

AV-380 Program in Cachexia Competition

Currently, in most markets globally, no agents have been approved for the treatment or prevention of cachexia caused by any disease, and few available treatments are effective in battling the symptoms, much less the underlying cause, of this wasting condition. Megace and medroxyprogesterone are approved for cancer cachexia in Europe, despite its low efficacy. Three agents have recently completed or are currently involved in Phase 3 trials. One agent, GTx, Inc. s selective androgen receptor modulator, or SARM, called enobosarm (GT-024) recently completed two Phase 3 trials for the prevention and treatment of muscle wasting in newly diagnosed locally advanced or metastatic non-small cell lung cancer patients. Another agent in Phase 3 trials is Helsinn s anamorelin, which is currently being studied in newly diagnosed locally advanced non-small cell lung cancer patients who have cachexia. A third agent, XBiotech s xilonix (MABp1), is in a Phase 3 trial for metastatic colorectal cancer patients who are cachectic and refractory to standard therapies.

A number of agents with different mechanisms of action are currently being studied in Phase 2 trials in cachexia or muscle wasting. Agents targeting the muscle regulatory molecule myostatin include Lilly s LY2495655, Regeneron s REGN-1033, and Atara Biosciences PINTA 745. Novartis is currently studying bimagrumab (BYM-338), an agent targeting the activin receptor. Drugs with other mechanisms currently in or recently completing Phase 2 clinical trials include Aeterna Zentaris macimorelin (ghrelin), Alder Biosciences clazakizumab (ALD-518, targeting IL-6), PsiOxus MT-102 (dual acting catabolic/anabolic transforming agent), Acacia s APD-209 (progestin/antagonist) and Ohr Pharmaceuticals OHR118 (cytoprotectant/immunomodulator).

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Strategic Partnerships

We have entered into multiple strategic partnerships in which we have in-licensed rights to compounds and granted rights to tivozanib, our antibody candidates and certain aspects of our Human Response Platform. Many of these agreements provide us with a source of cash flow in the form of up-front payments, equity investments, research and development funding, payments upon achievement of specified milestones, and potential royalties from product sales.

St. Vincent s Hospital

In July 2012, we entered into a license agreement with St. Vincent s Hospital Sydney Limited, which we refer to as St. Vincent s, under which we obtained an exclusive, worldwide license, with the right to grant sublicenses subject to certain restrictions, under specified patent rights and related know-how, to research, develop, manufacture and commercialize products for therapeutic applications that benefit from inhibition or decreased expression or activity of MIC-1, which is also known as GDF-15 and which we refer to throughout this Annual Report as GDF-15. We are exploiting this license in our AV-380 program for cachexia. We have a right of first negotiation to obtain an exclusive license to certain improvements that St. Vincent s or third parties may make to licensed therapeutic products. Under the license agreement, St. Vincent s also granted us non-exclusive rights for certain related diagnostic products and research tools.

Under the license agreement, we are obligated to use diligent efforts to conduct research and clinical development and commercially launch at least one licensed therapeutic product, and to maximize profits from licensed therapeutic products for the benefit of us and St. Vincent s. Subject to certain conditions, we have also agreed to achieve specified research, development and regulatory milestones by specified dates. If we do not achieve a given milestone by the agreed date, we have the option of paying the amount we would have been obligated to pay had we timely achieved the milestone, and, if we do so, St. Vincent s will not have the right to terminate the license agreement based on our failure to timely achieve such milestone.

We have also agreed that, for as long as there is a valid claim in the licensed patents, we will not, and we will ensure that our affiliates and our sublicensees do not, develop or commercialize any product, other than a licensed therapeutic product, for the treatment, prevention or prophylaxis of cachexia, decreased appetite or body weight, that binds to GDF-15 or the GDF-15 receptor and that is a GDF-15 antagonist, and will not license or induce any other person to do the same.

In connection with entering into the license agreement with St. Vincent s, we paid St. Vincent s an upfront license fee of $0.7 million and a low five-figure amount to reimburse St. Vincent s for patent-related expenses it incurred with respect to a specified licensed patent.

Under our license agreement with St. Vincent s, we may be required to:

- make milestone payments, up to an aggregate total of $9.2 million, upon achievement of specified research, development and regulatory milestones for the first three indications for licensed therapeutic products, some of which payments may be increased by a mid to high double-digit percentage rate for milestones payments made after we grant any sublicense under the license agreement, depending on the sublicensed territory or territories;

- pay tiered royalty payments equal to a low-single-digit percentage of any net sales we or our sublicensees make of licensed therapeutic products. The royalty rate escalates within the low-single-digit range during each calendar year based on increasing licensed therapeutic product sales during such calendar year. Our royalty payment obligations for a licensed therapeutic product in a particular country end on the later of 10 years after the date of first commercial sale of such licensed therapeutic product in such country or expiration of the last-to-expire valid claim of the licensed patents covering such licensed therapeutic product in such country, and are subject to offsets under certain circumstances;

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pay St. Vincent s sublicensing fees of up to an aggregate amount in the low-to-mid six-digits, depending on the sublicensed territory or territories, at the time we grant any sublicense; and

reimburse St. Vincent s for some or all of the reasonable costs and expenses it incurs in patent management, filing, prosecuting and maintaining the licensed patents.

The license agreement will remain in effect until the later of 10 years after the date of first commercial sale of licensed therapeutic products in the last country in which a commercial sale is made, or expiration of the last-to-expire valid claim of the licensed patents, unless we elect, or St. Vincent s elects, to terminate the license agreement earlier.

Either party has the right to terminate the agreement in connection with a material breach of the agreement by the other party that remains uncured for a specified cure period, or in connection with events relating to the other party s insolvency or bankruptcy, or if a force majeure event continues for more than 4 months.

St. Vincent s has the right to terminate the agreement due to any patent-related challenge by us, our affiliates or any sublicensee, or if we or our affiliates or any sublicensee cause or induce any other person to make a patent-related challenge, and such challenge continues after a specified cure period.

We have the right to terminate the agreement on 6 months notice if we terminate our GDF-15 research and development programs as a result of the failure of a licensed therapeutic product in pre-clinical or clinical development, or if we form the reasonable view that further GDF-15 research and development is not commercially viable, and we are not then in breach of any of our obligations under the agreement. If we form the reasonable view that further GDF-15 research and development is not commercially viable and terminate the agreement before we start a phase 1 clinical trial on a licensed therapeutic product, we will be required to pay St. Vincent s a low-to-mid six-figure termination payment.

We may also terminate the agreement on 60 days notice if certain licensed patents become invalid or unenforceable prior to July 2, 2014, are not in breach of any of our obligations under the agreement, and we, our affiliates and sublicensees have not made a patent-related challenge.

Any termination of the agreement, in whole or in part, will result in a loss of our rights to the relevant licensed patents and know-how. If St. Vincent s terminates the agreement in its entirety due to our breach, insolvency or a patent-related challenge, or we terminate the agreement due to a development failure or lack of commercial viability, as described above, St. Vincent s will have a non-exclusive license from us to certain intellectual property rights and know-how relating to the licensed therapeutic products, and we must transfer to St. Vincent s certain then-existing regulatory approvals and related documents for the licensed therapeutic products.

Kyowa Hakko Kirin

In December 2006, we entered into a license agreement with Kirin Brewery Co. Ltd. (now Kyowa Hakko Kirin) which we sometimes refer to as KHK, under which we obtained an exclusive license, with the right to grant sublicenses subject to certain restrictions, to research, develop, manufacture and commercialize tivozanib, pharmaceutical compositions thereof and associated biomarkers. Our exclusive license covers all territories in the world, except for Asia. KHK has retained rights to tivozanib in Asia. Under the license agreement, we obtained exclusive rights in our territory under certain KHK patents, patent applications and know-how related to tivozanib, to research, develop, make, have made, use, import, offer for sale, and sell tivozanib for the diagnosis, prevention and treatment of any and all human diseases and conditions. We and Kyowa Hakko Kirin each have access to and can benefit from the other party s clinical data and regulatory filings with respect to tivozanib and biomarkers identified in the conduct of activities under the license agreement.

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Under the license agreement, we are obligated to use commercially reasonable efforts to develop and commercialize tivozanib in our territory, including meeting certain specified diligence goals. Prior to the first anniversary of the first post-marketing approval sale of tivozanib in our territory, neither we nor any of our subsidiaries has the right to conduct certain clinical trials of, seek marketing approval for or commercialize any other cancer product that also works by inhibiting the activity of the VEGF receptor.

Upon entering into the license agreement with KHK, we made a one-time cash payment in the amount of $5.0 million. In addition, we are required to make various milestone payments which could total, in the aggregate, $60.0 million, including a milestone payment in connection with the TIVO-1 study and certain other milestone payments upon the achievement of specified regulatory milestones. In March 2010, we made a $10.0 million milestone payment to KHK in connection with the dosing of the first patient in our phase 3 clinical trial of tivozanib for the treatment of patients with advanced renal cell cancer, or RCC. We made a $22.5 million payment to KHK during the year ended December 31, 2011 related to the up-front license payment received under the collaboration and license agreement with Astellas which we entered into in February 2011. In December 2012, we made a $12.0 million milestone payment to KHK in connection with the acceptance by the FDA of our NDA filing for tivozanib for the treatment of patients with advanced RCC. We are also required to pay tiered royalty payments on net sales we make of tivozanib in our territory, which range from the low to mid teens as a percentage of net sales. The royalty rate escalates within this range based on increasing tivozanib sales. Our royalty payment obligations in a particular country in our territory begin on the date of the first commercial sale of tivozanib in that country and end on the later of 12 years after the date of first commercial sale of tivozanib in that country or the date of the last to expire of the patents covering tivozanib that have been issued in that country. In the event we sublicense the rights licensed to us under the license agreement, we are required to pay KHK a specified percentage of any amounts we receive from any third party sublicensees, other than amounts we receive in respect of research and development funding or equity investments, subject to certain limitations.

The license agreement will remain in effect until the expiration of all of our royalty and sublicense revenue obligations to Kyowa Hakko Kirin, determined on a product-by-product and country-by-country basis, unless we elect, or KHK elects, to terminate the license agreement earlier. If we fail to meet our obligations under the agreement and are unable to cure such failure within specified time periods, Kyowa Hakko Kirin can terminate the agreement, resulting in a loss of our rights to tivozanib and an obligation to assign or license to Kyowa Hakko Kirin any intellectual property or other rights we may have in tivozanib, including our regulatory filings, regulatory approvals, patents and trademarks for tivozanib.

Astellas Pharma

In February 2011, we entered into a collaboration and license agreement with Astellas and certain of its indirect wholly-owned subsidiaries in connection with which we and Astellas made plans to develop and seek to commercialize tivozanib for the treatment of a broad range of cancers. On February 12, 2014, Astellas exercised its right to terminate the agreement, as a result of the limited scope of development for tivozanib moving forward. The termination of the agreement will be effective August 11, 2014, at which time tivozanib rights will be returned to us. In accordance with the agreement, committed development costs, including the costs of winding down discontinued tivozanib clinical development programs, will be shared equally. There are no refund provisions in the agreement.

Under the terms of the collaboration agreement, we and Astellas shared responsibility for development and commercialization of tivozanib in the United States, Canada and Mexico, which we refer to collectively as North America, and Europe under a joint development plan and joint commercialization plan. Throughout the rest of the world (other than North America, Europe and Asia), which we refer to as the royalty territory, Astellas had an exclusive, royalty-bearing license to develop and commercialize tivozanib.

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In connection with the agreement, we received an initial cash payment of $125 million, comprised of a $75 million license fee and $50 million in research and development funding, both of which are non-creditable and non-refundable against any amounts due under the collaboration agreement. We retained net proceeds of approximately $97.6 million of the initial cash payment from Astellas, after payments to KHK and strategic, legal and financial advisors. In December 2012, we received a $15.0 million milestone payment from Astellas in connection with the acceptance by the FDA of our NDA filing for tivozanib for the treatment of patients with advanced RCC. We elected to recognize all milestone payments under the collaboration agreement as revenue once the milestones have been triggered if the milestone is deemed to be substantive.

Biogen Idec

In March 2009, we entered into an exclusive option and license agreement with Biogen Idec regarding the development and commercialization of our discovery-stage ErbB3-targeted antibodies for the potential treatment and diagnosis of cancer and other diseases in humans outside of North America. Under the agreement, we are responsible for developing ErbB3 antibodies through completion of the first phase 2 clinical trial designed in a manner that, if successful, will generate data sufficient to support advancement to a phase 3 clinical trial. Until a specified time after we complete this phase 2 clinical trial and deliver to Biogen Idec a detailed data package containing the results thereof, Biogen Idec may elect to obtain (1) a co-exclusive (with us), worldwide license, including the right to grant sublicenses, under our relevant intellectual property to develop and manufacture ErbB3 antibody products, and (2) an exclusive license, including the right to grant sublicenses, under our relevant intellectual property, to commercialize ErbB3 antibody products in all countries in the world other than North America. We retain the exclusive right to commercialize ErbB3 antibody products in North America. In this description, the countries in the world other than North America are referred to as Biogen Idec s territory, and North America is referred to as our territory. If Biogen Idec exercises its exclusive option to ErbB3 antibody products, Biogen Idec will grant us (a) a co-exclusive (with Biogen Idec), worldwide license under Biogen Idec s relevant intellectual property, to develop and manufacture ErbB3 antibody products anywhere in the world, and (b) an exclusive license under Biogen Idec s relevant intellectual property, to commercialize ErbB3 antibody products in North America.

If Biogen Idec exercises its option to obtain exclusive commercialization rights to ErbB3 products in its territory, we will then be solely responsible, subject to a mutually agreed development plan, budget and the oversight of a joint development committee, for the global development of ErbB3 antibody products, except that Biogen Idec will be solely responsible for ErbB3 antibody product development activities that relate solely to the Biogen Idec territory. Further, neither party has the right to conduct development activities in its respective territory if those development activities would materially and adversely affect the development of ErbB3 antibody products in the other party s territory. We and Biogen Idec will share global development costs (including manufacturing costs to support development) for ErbB3 antibody products equally, except that Biogen Idec will be solely responsible for all development costs associated solely with the development of ErbB3 antibody products for its territory, and we will be solely responsible for all development costs associated solely with the development of ErbB3 antibody products for North America. If either party wishes to develop a new ErbB3 antibody product under the agreement, and the other party does not also wish to develop that product, the party that desires to conduct development activities regarding the new ErbB3 antibody product has the right to independently, and at its sole cost, develop and manufacture the new ErbB3 antibody product for commercialization solely in its territory. If either party wishes to develop a ErbB3 antibody product for a new indication under the agreement, and the other party does not also wish to develop that product for such indication, the party that desires to conduct development activities regarding the new indication has the right to independently, and at its sole cost, develop and manufacture the new ErbB3 antibody product for such indication for commercialization solely in its territory, and the other party may elect, under specified circumstances, to pay to obtain rights to relevant clinical data to pursue regulatory approval for such indication in its territory.

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We have agreed that, prior to Biogen Idec s exercise of its exclusive option, or until the expiration of Biogen Idec s option right, we and our affiliates will not grant any third party rights to develop ErbB3 antibodies in our territory or in the Biogen Idec territory. We have also agreed that, during the term of the agreement, we will not grant any third party rights to develop or commercialize ErbB3 antibody products if such third party is independently developing or commercializing its own product containing an ErbB3 antibody. Prior to entering into discussions with, or granting a license or sublicense to, any third party with respect to the commercialization of ErbB3 antibody products, we are required to negotiate in good faith with Biogen Idec for a limited time period with respect to granting such rights to Biogen Idec. We have also agreed that, except pursuant to our agreement with Biogen Idec, during the term of the agreement, neither we nor our affiliates, alone or with or on behalf of any third party, will develop, manufacture or commercialize any ErbB3 antibody for therapeutic or diagnostic use in humans, or grant rights to any third party to do any of the foregoing.

If Biogen Idec fails to exercise its exclusive option to co-develop and commercialize ErbB3 antibody products, then the agreement will terminate on the date Biogen Idec s option right expires, and we will retain all of our rights to develop, manufacture and commercialize our ErbB3 antibody products. If Biogen Idec exercises its exclusive option to co-develop and commercialize ErbB3 antibody products, then, unless earlier terminated, the agreement will remain in effect until the last to expire of all royalty obligations under the agreement, or, if later, upon completion of any development activities that were pending before the expiration of all royalty obligations under the agreement.

If Biogen Idec terminates the agreement for convenience, or if we terminate the agreement due to a material breach of the agreement by Biogen Idec, in each case with respect to one or more ErbB3 antibody products after Biogen Idec s exercise of its exclusive option, then at our election, (1) Biogen Idec will lose all rights to the terminated product(s), (2) we will have the worldwide right to develop, manufacture and commercialize the terminated product(s), subject to milestone and royalty obligations to Biogen Idec in our territory and in the Biogen Idec territory, and (3) Biogen Idec will be required to transfer to us all regulatory approvals, data, promotional materials and other documents, materials and information reasonably necessary to enable us to develop, manufacture and commercialize the terminated products in the Biogen Idec territory. If Biogen Idec terminates the agreement due to our material breach of the agreement, at Biogen Idec s election (1) if not yet exercised, Biogen Idec will be deemed to have exercised its exclusive option and will not be required to pay us the option exercise fee, (2) Biogen Idec will have no further milestone payment obligations to us, (3) we will lose all rights to the terminated product(s), (4) Biogen Idec will have the worldwide right to develop, manufacture and commercialize the terminated product(s), subject to increased royalty obligations to us based on worldwide net sales, and (5) we will be required to transfer to Biogen Idec all regulatory approvals, data, promotional materials and other documents, materials and information reasonably necessary to enable Biogen Idec to develop, manufacture and commercialize the terminated products in our territory.

OSI Pharmaceuticals

In September 2007, we entered into a collaboration and license agreement with OSI Pharmaceuticals, Inc. (a wholly-owned subsidiary of Astellas US Holding Inc., a holding company owned by Astellas Pharma Inc.), or OSI. This strategic partnership is primarily focused on the identification and validation of genes and targets involved in the processes of epithelial-mesenchymal transition or mesenchymal-epithelial transition, in cancer. In July 2009, we expanded our strategic partnership with OSI and we granted OSI a non-exclusive license to use our proprietary bioinformatics platform, and non-exclusive, perpetual licenses to use bioinformatics data and to use a proprietary gene index related to a specific target pathway.

Under the July 2009 expanded agreement, if all applicable milestones are achieved, all remaining payments for the successful achievement of discovery, development and commercialization milestones under the agreement could total, in the aggregate, over $46.0 million, comprised of approximately (i) $8.4 million in substantive milestone payments upon achievement of specified clinical and development milestone events,

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(ii) $20.7 million in substantive milestone payments upon achievement of specified regulatory milestone events, and (iii) $17.5 million in milestone payments upon the achievement of specified sales amounts. In addition, we are eligible to receive up to $24.0 million in biomarker-related milestones.

In May 2012, we earned a patent-related milestone payment of $0.3 million upon filing of a patent application by OSI, and we also earned a clinical and development milestone payment of $0.8 million for commencement by OSI of GLP toxicology studies.

The next milestone payment that we may receive pursuant to this agreement is a $2.0 million clinical and development milestone for phase 1 clinical trial dosing. The next regulatory milestone payment we may receive pursuant to this agreement is $7.0 million to be achieved for the filing of an NDA with the FDA. We do not expect to achieve either of these milestones in the near future. Upon commercialization of products under the agreement, we are eligible to receive tiered royalty payments on sales of products by OSI, its affiliates and sublicensees.

The collaboration and license agreement will remain in effect until the expiration of both OSI s royalty obligations to us, and our royalty obligations to OSI, in each case determined on a product-by-product and country-by-country basis. Either party has the right to terminate the agreement in connection with a material breach of the agreement by the other party that remains uncured for a specified cure period. If OSI elects to terminate the agreement due to our material breach, we will lose our rights to certain intellectual property developed under the strategic partnership, and OSI will have the right to reduce its milestone and royalty obligations to us by the amount of monetary damages suffered by OSI as a direct result of our material breach. If we elect to terminate the agreement due to OSI s material breach of the agreement, OSI s licenses to all targets and products will terminate and revert to us, subject to our continued milestone and royalty payment obligations to OSI, which we will have the right to reduce by the amount of monetary damages we suffer as a direct result of OSI s breach. OSI may elect to terminate the agreement with respect to a particular collaboration target and all its associated products, in which event OSI s license to such target and products terminates and reverts to us, subject to our continued milestone and royalty payment obligations to OSI. For a specified time period after such termination, OSI and its affiliates may not, nor may they grant third parties the right to, conduct research or development activities with respect to the terminated collaboration target.

Intellectual Property Rights

Patent Rights

We have been building and intend to continue to build a strong intellectual property portfolio. We strive for multi-tiered patent protection, where possible. With respect to tivozanib, we have exclusively licensed patents that cover the molecule and its therapeutic use (patent expiration 2022, with the possibility of patent term extension to 2025 in the United States), a key step in manufacturing the molecule, and a crystal form of the molecule, i.e., a polymorph with low hygroscopicity used in the clinical formulation. With respect to tivozanib, we have:

U.S. patents: 3 issued; none pending; expirations ranging from 2018 to 2023

European patents: 3 granted; none pending; expirations ranging from 2018 to 2023

Canadian patents: 1 granted; none pending; expiration 2022

Australian patents: 1 granted; none pending; expiration 2022

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Complementing these in-licensed patents relating to tivozanib are two of our own issued U.S. patents that cover different biomarker tests for identifying human patients likely to respond to treatment with tivozanib, and an issued U.S. patent on a method of using tivozanib in combination with temsirolimus. With respect to tivozanib related technologies, we have:

U.S. patents: 3 issued; 1 pending; expirations ranging from 2029 to 2030

European patents: none granted; 2 pending; expirations ranging from 2029 to 2030

Canadian patents: none granted; 2 pending; expirations ranging from 2029 to 2030

Australian patents: none granted; 2 pending; expirations ranging from 2029 to 2030

International applications: 1 pending

With respect to GDF-15 antibodies, we have exclusively licensed a family of patents in the field of GDF-15 inhibition for therapeutic, preventative and palliative applications, including increasing appetite and/or body weight in subjects where decreased appetite and/or body weight loss due to elevated expression or amounts of GDF-15. Such patent expires in the United States in 2029 and in the European Union, if issued, in 2025.

With respect to the licensed technologies, we have:

U.S. patents: 3 issued; 3 pending; expirations ranging from 2016 to 2029

European patents: 2 granted; 3 pending; expirations ranging from 2016 to 2028

Japanese patents: 2 allowed; 3 pending; expirations ranging from 2021 to 2028.

Canadian patents: none granted; 4 pending; expiration 2016 to 2028

Australian patents: 3 granted; 2 pending; expiration 2016 to 2028

New Zealand: 1 granted; none pending; expiration 2016

Chinese patents: none granted; 1 pending; expiration 2028

Indian patents: none granted; 1 pending; expiration 2028

Complementing these in-licensed patents relating to GDF-15 inhibition, we have filed our own international patent application that covers our GDF antibodies. The patent, were it to be issued, would expire in 2033.

In addition to the to the above patents and patent applications related to tivozanib and GDF-15 antibodies, we own issued U.S. patents containing composition-of-matter claims that cover our HGF antibodies, including ficlatuzumab, our ErbB3 antibodies, our FGFR2 and FGFR3 antibodies, and our RON antibodies. In addition, we own pending patent applications covering our HGF antibodies, ErbB3 antibodies, FGFR2 antibodies, Notch 1 and Notch3 antibodies, and methods of making and using those antibodies. We are prepared to file patent applications on other antibodies in our antibody product pipeline soon after the experimental data necessary for an application becomes available. In addition, we own a pending patent application on use of a predictive biomarker for identifying patients likely to respond to one of our antibodies. We also own a granted U.S. patent and pending foreign counterpart patent applications covering a method of identifying cancer tissue likely to be sensitive or resistant to treatment with an inhibitor of Notch receptor activation. With respect to our antibody product pipeline, we have:

U.S. patents: 13 issued; 6 pending; expirations ranging from 2027 to 2031

European patents: 2 granted; 4 pending; expirations ranging from 2027 to 2031

Japanese patents: 2 granted; 5 pending; expirations ranging from 2027 to 2031

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Canadian patents: none granted; 5 pending; expirations ranging from 2027 to 2031

Australian patents: 2 granted; 3 pending; expirations ranging from 2027 to 2031

International applications: 3 pending

In addition to patents relating to tivozanib, GDF-15, ficlatuzumab, AV-203 and other therapeutic antibodies in our product pipeline, our patent portfolio contains a number of other patents and patent applications relevant to our business. We own a granted U.S. patent and issued foreign counterparts covering a method of making a chimeric mouse cancer model. We also own a granted U.S. patent and issued foreign counterparts covering a method of producing primary tumor material via directed complementation. We also own a granted U.S. patent and pending U.S. and foreign patent applications covering a mouse model that contains a human breast tumor. We own pending patent applications that cover a general method for identifying new, multi-gene biomarkers for predicting response to an anti-cancer drug of interest, as well as specific multi-gene biomarkers identified by using the same method. With respect to our technology platforms, we have:

U.S. patents: 5 issued; 3 pending; expirations ranging from 2020 to 2032

European patents: 3 granted; 2 pending; expirations ranging from 2022 to 2026

Japanese patents: 3 granted; 1 pending; expirations ranging from 2022 to 2026

Canadian patents: 2 granted; none pending; expirations ranging from 2022 to 2026

Australian patents: 4 granted; none pending; expirations ranging from 2022 to 2026

International applications: 2 pending.

In addition to filing and prosecuting patent applications in the United States, we file counterpart patent applications in Europe, Canada, Japan, Australia (and sometimes additional countries), in cases where we think such foreign filing is likely to be cost-effective.

The term of individual patents depends upon the legal term of the patents in the countries in which they are obtained. In most countries in which we file, the patent term is 20 years from the earliest date of filing a non-provisional patent application. In the United States, a patent s term may be lengthened by patent term adjustment, which compensates a patentee for administrative delays by the U.S. Patent and Trademark Office in granting a patent. A U.S. patent term may be shortened, if a patent is terminally disclaimed by its owner, over another patent.

The patent term of a patent that covers an FDA-approved drug may also be eligible for patent term extension, which permits patent term restoration as compensation for the patent term lost during the FDA regulatory review process. The Drug Price Competition and Patent Term Restoration Act of 1984, or the Hatch-Waxman Act, permits a patent term extension of up to five years beyond the expiration of the patent. The length of the patent term extension is related to the length of time the drug is under regulatory review. Patent extension cannot extend the remaining term of a patent beyond a total of 14 years from the date of product approval, and only one patent applicable to an approved drug may be extended. Similar provisions are available in Europe and other foreign jurisdictions to extend the term of a patent that covers an approved drug. In the future, if and when our pharmaceutical products receive FDA approval, we expect to apply for patent term extensions on patents covering those products.

Many pharmaceutical companies, biotechnology companies and academic institutions are competing with us in the field of oncology and filing patent applications potentially relevant to our business. In order to contend with the inevitable possibility of third party intellectual property conflicts, we make freedom-to-operate studies an ongoing part of our business operations. With regard to tivozanib, we are aware of a third party United States patent, and corresponding foreign counterparts, that contain broad claims related to the use of an organic compound that, among

other things, inhibits tyrosine phosphorylation of a VEGF receptor caused by VEGF binding to such VEGF receptor. We are also aware of third party United States patents that contain broad claims related to the use of a tyrosine kinase inhibitor in combination with a DNA damaging agent such as

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chemotherapy or radiation and we have received written notice from the owners of such patents indicating that they believe we may need a license from them in order to avoid infringing their patents. With regard to ficlatuzumab, we are aware of two separate families of United States patents, United States patent applications and foreign counterparts, with each of the two families being owned by a different third party, that contain broad claims related to anti-HGF antibodies having certain binding properties and their use. With regard to GDF-15, we are aware of a third-party United States patent that contains broad claims related to antibodies binding to the GDF-15 protein, which patent is set to expire in 2014. With regard to AV-203, we are aware of a third party United States patent that contains broad claims relating to anti-ErbB3 antibodies. Based on our analyses, if any of the above third party patents were asserted against us, we do not believe our proposed products or activities would be found to infringe any valid claim of these patents. If we were to challenge the validity of any issued United States patent in court, we would need to overcome a statutory presumption of validity that attaches to every United States patent. This means that in order to prevail, we would have to present clear and convincing evidence as to the invalidity of the patent s claims. There is no assurance that a court would find in our favor on questions of infringement or validity.

From time to time, we find it necessary or prudent to obtain licenses from third party intellectual property holders. Where licenses are readily available at reasonable cost, such licenses are considered a normal cost of doing business. In other instances, however, we may use the results of freedom-to-operate studies to guide our early-stage research away from areas where we are likely to encounter obstacles in the form of third party intellectual property. For example, where a third party holds relevant intellectual property and is a direct competitor, a license might not be available on commercially reasonable terms or available at all. We strive to identify potential third party intellectual property issues in the early stages of research of our research programs, in order to minimize the cost and disruption of resolving such issues.

In spite of these efforts to avoid obstacles and disruptions arising from third party intellectual property, it is impossible to establish with certainty that our technology platform or our product programs will be free of claims by third party intellectual property holders. Even with modern databases and on-line search engines, literature searches are imperfect and may fail to identify relevant patents and published applications. Even when a third party patent is identified, we may conclude upon a thorough analysis, that we do not infringe the patent or that the patent is invalid. If the third party patent owner disagrees with our conclusion and we continue with the business activity in question, patent litigation may be initiated against us. Alternatively, we might decide to initiate litigation in an attempt to have a court declare the third party patent invalid or non-infringed by our activity. In either scenario, patent litigation typically is costly and time-consuming, and the outcome is uncertain. The outcome of patent litigation is subject to uncertainties that cannot be quantified in advance, for example, the credibility of expert witnesses who may disagree on technical interpretation of scientific data. Ultimately, in the case of an adverse outcome in litigation, we could be prevented from commercializing a product or using certain aspects of our technology platform as a result of patent infringement claims asserted against us. This could have a material adverse effect on our business.

To protect our competitive position, it may be necessary to enforce our patent rights through litigation against infringing third parties. Litigation to enforce our own patent rights is subject to the same uncertainties discussed above. In addition, however, litigation involving our patents carries the risk that one or more of our patents will be held invalid (in whole or in part, on a claim-by-claim basis) or held unenforceable. Such an adverse court ruling could allow third parties to commercialize our products or our platform technology, and then compete directly with us, without making any payments to us.

Trade Secrets

For some aspects of our proprietary technology, trade secret protection is more appropriate than patent protection. For example, our proprietary bioinformatics software tools and databases are protected as trade

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secrets. Our bioinformatics tools and databases give us the means to store, analyze, interpret and integrate the large volume of data generated from our various tumor models and from analysis of human clinical samples from clinical trials. We continually make incremental improvements in our proprietary software tools, as we tailor them to the changing needs of our research and development programs. In general, trade secret protection can accommodate this continuing evolution of our bioinformatics system better than other forms of intellectual property protection.

Trademarks

We seek trademark protection in the U.S. and foreign jurisdictions where available and when appropriate. We have filed to register several trademarks intended for potential use in the marketing of tivozanib. We own a U.S. trademark that we use in connection with our research and development (Human Response Platform). We also own a U.S. trademark (The Human Response) and a U.S. trademark application (AVEO Oncology The Human Response) that we use in connection with our business, in general.

Manufacturing

We currently contract with third parties for the manufacture of clinical, to the extent we require, and commercial quantities of our product candidates and intend to do so in the future. We do not own or operate manufacturing facilities for the production of clinical or commercial quantities of our product candidates. We currently have no plans to build our own clinical or commercial scale manufacturing capabilities. Although we rely on contract manufacturers, we have personnel with extensive manufacturing experience to oversee the relationships with our contract manufacturers.

One of our contract manufacturers has manufactured what we believe to be sufficient quantities of tivozanib s drug substance to support our ongoing clinical trials. In addition, we currently engage a separate contract manufacturer to manufacture, package and distribute clinical supplies of tivozanib.

As of December 27, 2010, the effective date of the termination of our collaboration with Merck relating to ficlatuzumab, we became responsible for all process development and all manufacturing of ficlatuzumab for future development and commercialization. Prior to Merck s termination of its collaboration agreement with us, multiple batches of drug product were produced by Merck to support clinical trials of ficlatuzumab through phase 2 clinical trials. In November 2011, we entered into an agreement with Boehringer Ingelheim for large-scale process development and clinical manufacturing of ficlatuzumab. In connection with the agreement, Boehringer Ingelheim is producing ficlatuzumab at its biopharmaceutical sites in Fremont, CA (drug substance) and Biberach, Germany (drug product).

In August 2010, we entered into an agreement with Gallus BioPharmaceuticals, LLC (previously known as Laureate Pharma, Inc.), or Gallus, for the clinical manufacture of AV-203 drug substance. Gallus has produced two batches of AV-203 drug substance for clinical trials at its site in Princeton, NJ. AV-203 drug product is produced at Microtest Laboratories, Inc. in Agawam, Massachusetts.

On March 9, 2014, we entered into a manufacturing agreement with AbbVie Inc. for the process and development of AV-380.

To date, our third-party manufacturers have met our manufacturing requirements. We believe that there are alternate sources of supply that can satisfy our clinical and commercial requirements, although we cannot be certain that identifying and establishing relationships with such sources, if necessary, would not result in significant delay or material additional costs.

Government Regulation

Government authorities in the United States (including federal, state and local authorities) and in other countries, extensively regulate, among other things, the manufacturing, research and clinical development,

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marketing, labeling and packaging, distribution, post-approval monitoring and reporting, advertising and promotion, and export and import of pharmaceutical products, such as those we are developing. The process of obtaining regulatory approvals and the subsequent compliance with appropriate federal, state, local and foreign statutes and regulations require the expenditure of substantial time and financial resources.

United States Government Regulation

In the United States, the FDA regulates drugs under the Federal Food, Drug, and Cosmetic Act, or FDCA, and related regulations. Drugs are also subject to other federal, state and local statutes and regulations. Biological products are subject to regulation by the FDA under the FDCA, the Public Health Service Act, and related regulations, and other federal, state and local statutes and regulations. Failure to comply with the applicable U.S. regulatory requirements at any time during the product development process, approval process or after approval, may subject an applicant to administrative or judicial sanctions. These sanctions could include the imposition by the FDA or an Institutional Review Board, or IRB, of a clinical hold on trials, the FDA s refusal to approve pending applications or supplements, withdrawal of an approval, warning letters, product recalls, product seizures, total or partial suspension of production or distribution, injunctions, fines, civil penalties or criminal prosecution. Any agency or judicial enforcement action could have a material adverse effect on us.

The Investigational New Drug Process

An Investigational New Drug application, or an IND, is a request for authorization from the FDA to administer an investigational drug or biological product to humans. Such authorization must be secured prior to interstate shipment (usually to clinical investigators) and administration of any new drug or biological product to humans that is not the subject of an approved New Drug Application or Biologics License Application, except under limited circumstances.

To conduct a clinical investigation with an investigational new drug or biological product, we are required to file an IND with the FDA in compliance with Title 21 of the Code of Federal Regulations (CFR), Part 312. These regulations contain the general principles underlying the IND submission and the general requirements for an IND s content and format.

The central focus of the initial IND submission is on the general investigational plan and the protocol(s) for human studies. The IND also includes results of animal studies or other human studies, as appropriate, as well as manufacturing information, analytical data and any available clinical data or literature to support the use of the investigational new drug or biological product. An IND must become effective before human clinical trials may begin. An IND will automatically become effective 30 days after receipt by the FDA, unless before that time the FDA raises concerns or questions related to the proposed clinical trials as outlined in the IND. In such a case, the IND may be placed on clinical hold and the IND sponsor and the FDA must resolve any outstanding concerns or questions before clinical trials can begin. Accordingly, submission of an IND may or may not result in the FDA allowing clinical trials to commence.

Clinical trials involve the administration of the investigational drug or biological product to patients under the supervision of qualified investigators in accordance with Good Clinical Practices, or GCPs. Clinical trials are conducted under protocols detailing, among other things, the objectives of the study, the parameters to be used in monitoring safety, and the efficacy criteria to be evaluated. A protocol for each clinical trial and any subsequent protocol amendments must be submitted to the FDA as part of the IND. Additionally, approval must also be obtained from each clinical site s independent IRB before the trials may be initiated. All participants in our clinical trials must provide their informed consent in writing in compliance with GCPs and the ethical principles that have their origin in the Declaration of Helsinki.

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The clinical investigation of an investigational drug or biological product is generally divided into three phases. Although the phases are usually conducted sequentially, they may overlap or be combined. The three phases of an investigation are as follows:

Phase 1. Phase 1 includes the initial introduction of an investigational new drug or biological product into humans. Phase 1 clinical trials are typically closely monitored and may be conducted in patients with the target disease or condition or healthy volunteers. These studies are designed to evaluate the safety, dosage tolerance, metabolism and pharmacologic actions of the investigational drug or biological product in humans, the side effects associated with increasing doses, and if possible, to gain early evidence on effectiveness. During phase 1 clinical trials, sufficient information about the investigational drug s or biological product s pharmacokinetics and pharmacological effects may be obtained to permit the design of well-controlled and scientifically valid phase 2 clinical trials. The total number of participants included in phase 1 clinical trials varies, but is generally in the range of 20 to 80.

Phase 2. Phase 2 includes the controlled clinical trials conducted to preliminarily or further evaluate the effectiveness of the investigational drug or biological product for a particular indication(s) in patients with the disease or condition under study, to determine dosage tolerance and optimal dosage, and to identify possible adverse side effects and safety risks associated with the drug or biological product. Phase 2 clinical trials are typically well-controlled, closely monitored, and conducted in a limited patient population, usually involving no more than several hundred participants.

Phase 3. Phase 3 clinical trials are generally controlled clinical trials conducted in an expanded patient population generally at geographically dispersed clinical trial sites. They are performed after preliminary evidence suggesting effectiveness of the drug or biological product has been obtained, and are intended to further evaluate dosage, clinical effectiveness and safety, to establish the overall benefit-risk relationship of the investigational drug or biological product, and to provide an adequate basis for product approval. Phase 3 clinical trials usually involve several hundred to several thousand participants.

The FDA s primary objectives in reviewing an IND are to assure the safety and rights of patients and to help assure that the quality of the investigation will be adequate to permit an evaluation of the drug s effectiveness and safety and of the biological product s safety, purity and potency. The decision to terminate development of an investigational drug or biological product may be made by either a health authority body such as the FDA, an IRB or ethics committee, or by us for various reasons. Additionally, some trials are overseen by an independent group of qualified experts organized by the trial sponsor, known as a data safety monitoring board or committee. This group provides authorization for whether or not a trial may move forward at designated check points based on access that only the group maintains to available data from the study. Suspension or termination of development during any phase of clinical trials can occur if it is determined that the participants or patients are being exposed to an unacceptable health risk. Other reasons for suspension or termination may be made by us based on evolving business objectives and/or competitive climate.

In addition, there are requirements and industry guidelines that require the posting of ongoing clinical trials on public registries, and the disclosure of designated clinical trial results.

The NDA/BLA Approval Process

In order to obtain approval to market a drug or biological product in the United States, a marketing application must be submitted to the FDA that provides data establishing the safety and effectiveness of the drug product for the proposed indication, and the safety, purity and potency of the biological product for its intended indication. The application includes all relevant data available from pertinent preclinical and clinical trials, including negative or ambiguous results as well as positive findings, together with detailed information relating to the product s chemistry, manufacturing, controls and proposed labeling, among other things. Data can come

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from company-sponsored clinical trials intended to test the safety and effectiveness of a use of a product, or from a number of alternative sources, including studies initiated by investigators. To support marketing approval, the data submitted must be sufficient in quality and quantity to establish the safety and effectiveness of the investigational drug product and the safety, purity and potency of the biological product to the satisfaction of the FDA.

The steps required before an investigational drug or biological product may be marketed in the United States generally include:

- Completion of preclinical laboratory tests, animal studies and formulation studies in compliance with the FDA s Good Laboratory Practices, or GLP, regulations;
- Submission to the FDA of an IND to support human clinical testing;
- Approval by an IRB at each clinical site before each trial may be initiated;
- Performance of adequate and well-controlled clinical trials in accordance with GCP to establish the safety and efficacy of the investigational drug product for each targeted indication or the safety, purity and potency of the biological product for its intended indication;
- Submission of an NDA or Biologics License Application, or BLA, to the FDA;
- Satisfactory completion of an FDA Advisory Committee review, if applicable;
- Satisfactory completion of an FDA inspection of the manufacturing facilities at which the investigational drug or biological product is produced to assess compliance with current good manufacturing practices, or cGMP, and to assure that the facilities, methods and controls are adequate to preserve the product s identity, strength, quality and purity; and
- FDA review and approval of the NDA or BLA.

In most cases, the NDA or BLA must be accompanied by a substantial user fee; there may be some instances in which the user fee is waived.

The FDA will initially review the NDA or BLA for completeness before it accepts the NDA or BLA for filing. The FDA has 60 days from its receipt of an NDA or BLA to determine whether the application will be accepted for filing based on the agency s threshold determination that it is sufficiently complete to permit substantive review. After the NDA submission is accepted for filing, the FDA reviews the NDA to determine, among other things, whether the proposed product is safe and effective for its intended use, and whether the product is being manufactured in accordance with cGMP to assure and preserve the product s identity, strength, quality and purity. After the BLA submission is accepted for filing, the FDA reviews the BLA to determine, among other things, whether the product is safe, pure and potent and the facility in which it is manufactured, processed, packaged or held meets standards designed to assure the product s continued safety, purity and potency. The FDA may refer applications for novel drug or biological products or drug or biological products that present difficult questions of safety or efficacy to an advisory committee, typically a panel that includes outside clinicians and other experts, for review, evaluation and a recommendation as to whether the application should be approved and under what conditions. The FDA is not bound by the recommendations of an advisory committee, but it considers such recommendations carefully when making decisions.

Before approving an NDA or BLA, the FDA will carefully review and typically require changes to the proposed product labeling. The FDA will also inspect the facilities at which the product is manufactured. The FDA will not approve the product unless it determines that the manufacturing processes and facilities are in compliance with cGMP requirements and adequate to assure consistent production of the product within required specifications. Additionally, before approving an NDA or BLA, the FDA will typically inspect one or more clinical sites to

assure compliance with GCP. If the FDA determines the application, manufacturing process or manufacturing facilities are not acceptable, it will outline the deficiencies in the submission and often will request additional testing or information. Notwithstanding the submission of any requested additional information, the FDA ultimately may decide that the application does not satisfy the regulatory criteria for approval.

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The testing and approval process requires substantial time, effort and financial resources, and each may take several years to complete. Data obtained from clinical activities are not always conclusive and may be susceptible to varying interpretations, which could delay, limit or prevent regulatory approval. The FDA may not grant approval on a timely basis, or at all. We may encounter difficulties or unanticipated costs in our efforts to develop our product candidates and secure necessary governmental approvals, which could delay or preclude us from marketing our products. Even if the FDA approves a product, it may limit the approved indications for use, impose prominent warnings, or place other conditions on any approvals that could restrict the commercial application of the products such as a requirement that we implement special risk management measures through a Risk Evaluation and Mitigation Strategy. After approval, some types of changes to the approved product, such as adding new indications, manufacturing changes and additional labeling claims, are subject to further testing requirements and FDA review and approval.

Post-Approval Regulation

After regulatory approval of a drug or biological product is obtained, we are required to comply with a number of post-approval requirements. For example, as a condition of approval of an NDA or BLA, the FDA may require post-marketing testing, including phase 4 clinical trials, and surveillance to further assess and monitor the product s safety and effectiveness after commercialization. Regulatory approval of oncology products often requires that patients in clinical trials be followed for long periods to determine the overall survival benefit of the drug or biologic. In addition, as a holder of an approved NDA or BLA, we would be required to report, among other things, certain adverse events and production problems to the FDA, to provide updated safety and efficacy information, and to comply with requirements concerning advertising and promotional labeling for any of our products. Also, quality control and manufacturing procedures must continue to conform to cGMP after approval to assure and preserve the long term stability of the drug or biological product. The FDA periodically inspects manufacturing facilities to assess compliance with cGMP, which imposes extensive procedural, substantive and record keeping requirements. In addition, changes to the manufacturing process are strictly regulated, and, depending on the significance of the change, may require prior FDA approval before being implemented. FDA regulations also require investigation and correction of any deviations from cGMP and impose reporting and documentation requirements upon us and any third party manufacturers that we may decide to use. Accordingly, manufacturers must continue to expend time, money and effort in the area of production and quality control to maintain compliance with cGMP and other aspects of regulatory compliance.

We rely, and expect to continue to rely, on third parties for the production of clinical and commercial quantities of our product candidates. Future FDA, foreign regulatory authorities, and state inspections may identify compliance issues at our facilities or at the facilities of our contract manufacturers that may disrupt production or distribution, or require substantial resources to correct. In addition, discovery of previously unknown problems with a product or the failure to comply with applicable requirements may result in restrictions on a product, manufacturer or holder of an approved NDA or BLA, including withdrawal or recall of the product from the market or other voluntary, FDA-initiated or judicial action that could delay or prohibit further marketing. Newly discovered or developed safety or effectiveness data may require changes to a product s approved labeling, including the addition of new warnings and contraindications, and also may require the implementation of other risk management measures.

Also, new government requirements, including those resulting from new legislation, may be established, or the FDA s policies may change, which could delay or prevent regulatory approval of our products under development and/or could significantly impact the requirements imposed on us after approval.

Europe / Rest of World Government Regulation

In addition to regulations in the United States, we will be subject to a variety of regulations in other jurisdictions governing, among other things, clinical trials and any commercial sales and distribution of our products.

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Whether or not we obtain FDA approval for a product, we must obtain the requisite approvals from regulatory authorities in foreign countries prior to the commencement of clinical trials or marketing of the product in those countries. Certain countries outside of the United States have a similar process that requires the submission of a clinical trial application much like the IND prior to the commencement of human clinical trials. In the European Union, for example, a clinical trial application, or CTA, must be submitted to each country s national health authority and an independent ethics committee, much like the FDA and IRB, respectively. Once the CTA is approved in accordance with a country s requirements, and relevant ethics committees have issued positive opinions, the clinical trial covered by the CTA may proceed. In all cases, the clinical trials must be conducted in accordance with GCP and the applicable regulatory requirements and the ethical principles that have their origin in the Declaration of Helsinki.

To obtain regulatory approval of an investigational drug or biological medicinal product under European Union regulatory systems, we must submit a marketing authorization application. The application used to file the NDA or BLA in the United States is similar to that required in Europe, with the exception of, among other things, country-specific documentation requirements. The requirements and process governing pricing and reimbursement in the European Union vary from country to country.

For other countries outside of the European Union, such as countries in Latin America or Asia, the requirements governing the conduct of clinical trials, product licensing, pricing and reimbursement vary from country to country. In all cases, again, any clinical trials that we sponsor must be conducted in accordance with GCP and the applicable regulatory requirements and the ethical principles that have their origin in the Declaration of Helsinki.

If we fail to comply with applicable foreign regulatory requirements, we may be subject to, among other things, fines, suspension or withdrawal of regulatory approvals, product recalls, seizure of products, operating restrictions and criminal prosecution.

Compliance

During all phases of development (pre- and post-marketing), failure to comply with the applicable regulatory requirements may result in administrative or judicial sanctions. These sanctions could include the FDA s imposition of a clinical hold on trials or the suspension of clinical trials by other regulatory authorities, refusal to approve pending applications, withdrawal of an approval, warning letters, product recalls, product seizures, total or partial suspension of production or distribution, product detention or refusal to permit the import or export of products, injunctions, fines, civil penalties or criminal prosecution. Any agency or judicial enforcement action could have a material adverse effect on us.

Available Special Regulatory Procedures

Formal Meetings

We are encouraged to engage and seek guidance from health authorities relating to the development and review of investigational drugs and biologics, as well as marketing applications. In the United States, there are different types of official meetings that may occur between us and the FDA. Each meeting type is subject to different procedures. Conclusions and agreements from each of these meetings are captured in the official final meeting minutes issued by the FDA.

The EMA and national medicines regulators within the EU also provide the opportunity for dialogue with us. At the EMA level, this is usually done in the form of Scientific Advice, which is given by the Scientific Advice Working Party of the Committee for Medicinal Products for Human Use, or CHMP. A fee is incurred with each Scientific Advice procedure.

Advice from either the FDA or EMA is typically provided based on questions concerning, for example, quality (chemistry, manufacturing and controls testing), nonclinical testing and clinical studies, and pharmacovigilance plans and risk-management programs. Advice is not legally binding with regard to any future

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marketing authorization application of the product concerned. To obtain binding commitments from the FDA on the design and size of clinical trials intended to form the primary basis of an effectiveness claim, Special Protocol Assessment procedures are available. Where the FDA agrees to a Special Protocol Assessment, or SPA, the agreement may not be changed by either the sponsor or the FDA except if the sponsor and the FDA agree to a change, or a senior FDA official determines that a substantial scientific issue essential to determining the safety or effectiveness of the product was identified after the testing began. An SPA is not binding if new circumstances arise, and there is no guarantee that a study will ultimately be adequate to support an approval even if the study is conducted according to the terms of an SPA.

Orphan Drug Designation

The FDA may grant orphan drug designation to drugs and biological products intended to treat a rare disease or condition that affects fewer than 200,000 individuals in the United States, or if it affects more than 200,000 individuals in the United States and there is no reasonable expectation that the cost of developing and making the drug or biological product for this type of disease or condition will be recovered from sales in the United States. In the European Union, the EMA s Committee for Orphan Medicinal Products, or COMP, may recommend orphan drug designation to promote the development of products that are intended for the diagnosis, prevention or treatment of life-threatening or chronically debilitating conditions affecting not more than 5 in 10,000 persons in the European Union. Additionally, designation is granted for products intended for the diagnosis, prevention or treatment of a life-threatening, seriously debilitating or serious and chronic condition and when, without incentives, it is unlikely that sales of the drug in the European Union would be sufficient to justify the necessary investment in developing the drug or biological product. In addition, the COMP may only recommend orphan drug designation when the product in question offers a significant clinical benefit over existing approved products for the relevant indication. Following a positive opinion by the COMP, the European Commission adopts a decision granting orphan status. The COMP will reassess orphan status in parallel with EMA review of a marketing authorization application and orphan status may be withdrawn at that stage if it no longer fulfills the orphan criteria.

In the United States, orphan drug designation entitles a party to financial incentives such as opportunities for grant funding towards clinical trial costs, tax advantages and user-fee waivers. In addition, if a product receives the first FDA approval for the indication for which it has orphan designation, the product is entitled to orphan drug exclusivity, which means the FDA may not approve any other application to market the same drug or biological product for the same indication for a period of 7 years, except in limited circumstances, such as a showing of clinical superiority over the product with orphan exclusivity or if the product with orphan exclusivity experiences a shortage.

In the European Union, orphan drug designation also entitles a party to financial incentives such as reduction of fees or fee waivers and 10 years of market exclusivity is granted following drug or biological product approval. During this period, regulators may not accept or approve any similar medicinal product, unless it offers a significant clinical benefit. This period may be reduced to 6 years if the orphan drug designation criteria are no longer met, including where it is shown that the product is sufficiently profitable not to justify maintenance of market exclusivity.

Orphan drug designation must be requested before submitting an application for marketing approval. Orphan drug designation does not convey any advantage in, or shorten the duration of, the regulatory review and approval process.

Pediatric Development

In the United States, Section 505A of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 355a, Pediatric Studies of Drugs) provides for an additional 6 months of marketing exclusivity for a drug if reports are filed of investigations studying the use of the drug product in a pediatric population in response to a written request from

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the FDA. Separate from this potential exclusivity benefit, NDAs and BLAs must contain data (or a proposal for post-marketing activity) to assess the safety and effectiveness of an investigational drug or biological product for the claimed indications in all relevant pediatric populations in order to support dosing and administration for each pediatric subpopulation for which the drug is safe and effective. The FDA may, on its own initiative or at the request of the applicant, grant deferrals for submission of some or all pediatric data until after approval of the product for use in adults or full or partial waivers if certain criteria are met. Discussions about pediatric development plans can be discussed with the FDA at any time, but usually occur any time between the end-of-phase 2 meeting and submission of the NDA or BLA.

For the EMA, a Pediatric Investigation Plan, and/or a request for waiver or deferral, is required for submission prior to submitting a marketing authorization application.

Authorization Procedures in the European Union

There are two types of marketing authorization procedures for medicinal products in the European Union; the centralized authorization procedure and national authorization procedures.

Centralized procedure. The centralized procedure gives rise to marketing authorizations that are valid throughout the European Union and, by extension, in three European Economic Area, or EEA member states, Norway, Iceland and Liechtenstein. Applicants file marketing authorizations with the EMA, where they are reviewed by a relevant scientific committee, which is most likely the Committee for Medicinal Products for Human Use, or CHMP. The EMA forwards CHMP positive opinions to the European Commission, which uses them as the basis for a decision granting a marketing authorization. The centralized procedure is compulsory for human medicines that are: derived from biotechnology processes, such as recombinant DNA technology, controlled expression of genes in prokaryotes and eukaryotes and hybridoma and monoclonal antibody methods. It is also mandatory for products containing a new active substance indicated for the treatment of certain diseases, such as HIV/AIDS, cancer, diabetes, neurodegenerative disorders, viral diseases or autoimmune diseases and other immune dysfunctions, and officially designated orphan medicines. For medicines that do not fall within these categories, an applicant has the option of submitting an application for a centralized marketing authorization to the EMA, as long as the CHMP accepts that the medicine concerned is a significant therapeutic, scientific or technical innovation, or if its authorization would be in the interest of public health.

National authorization procedures. There are also two other possible routes to authorize medicinal products in more than one EU or EEA country, which are available for investigational drug products that fall outside the scope of the centralized procedure:

Decentralized procedure. Using the decentralized procedure, an applicant may apply for simultaneous authorization in more than one EEA country of medicinal products that have not yet been authorized in any EEA country and that do not fall within the mandatory scope of the centralized procedure. The applicant selects a so-called reference member state, or RMS, to take the lead in the review of the application. Other member states are expected to recognize the RMS decision, unless they identify a serious risk to public health. If the member states cannot resolve any such concerns between themselves, the matter is referred to the CHMP for an opinion and ultimately a binding European Commission decision.

Mutual recognition procedure. In the mutual recognition procedure, a medicine is first authorized in one EEA RMS, in accordance with the national procedures of that country. Following this, further marketing authorizations can be sought from other EEA countries in a procedure whereby the countries concerned agree to recognize the validity of the original, national marketing authorization. As in the decentralized procedure, these concerned member states must recognize the RMS approval unless they identify a serious risk to the public health. If the member states cannot reach a consensus between themselves, the matter can be referred to the CHMP.

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Priority Review / Standard Review (United States) and Accelerated Review (European Union)

Based on results of phase 3 clinical trials, an NDA or BLA may receive either priority or standard review from the FDA. Priority review is given where preliminary estimates indicate that a product, if approved, would provide a significant improvement in safety or effectiveness of the treatment, diagnosis or prevention of a serious condition. Under PDUFA V, effective October 1, 2012, where an application receives priority review, the target date for FDA action will be 8 months from submission in the case of an application for a new chemical entity and 6 months from submission in the case of products that do not contain a new chemical entity. Where an application receives standard review, the target date for FDA action will be 12 months from submission in the case of an application for a new chemical entity and 10 months from submission in the case of products that do not contain a new chemical entity.

Under the centralized procedure in the European Union, the maximum timeframe for the evaluation of a marketing authorization application is 210 days (excluding clock stops, when additional written or oral information is to be provided by the applicant in response to questions asked by the CHMP). Accelerated evaluation might be granted by the CHMP in exceptional cases, when a medicinal product is expected to be of a major public health interest, defined by three cumulative criteria: the seriousness of the disease (e.g. heavy disabling or life-threatening diseases) to be treated; the absence or insufficiency of an appropriate alternative therapeutic approach; and anticipation of high therapeutic benefit. In this circumstance, EMA ensures that the opinion of the CHMP is given within 150 days.

Biosimilars

The 2010 healthcare reform legislation created an approval pathway for biosimilars (i.e., follow-on version of innovative biologics). The European regulatory bodies also have authority to approve biosimilars. Because many issues under the U.S. biosimilar legislation remain unresolved (including the scope of exclusivity for new biologics), it is difficult to predict how this legislation will affect us. Our products may face significant competition from biosimilars (as well as traditional generic drugs) in the United States and abroad.

Employees

As of December 31, 2013, we had 71 employees worldwide. None of our employees is represented by a labor union or is covered by a collective bargaining agreement. We consider our relationship with our employees to be good.

Research and Development Costs

Our research and development costs were $68.5 million, $91.4 million, and $101.7 million for the years ended December 31, 2013, 2012 and 2011, respectively. These costs consist of the cost of our own independent research and development efforts and the costs associated with collaborative research and development and in-licensing arrangements. Research and development costs, including upfront fees and milestones paid to collaboration partners, are expensed as incurred if the underlying products have not received regulatory approval and have no alternative future use.

Segment and Geographic Information

We view our operations and manage our business in one operating segment. As of December 31, 2013, we operate only in the United States.

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Executive Officers

The following table lists the positions, names and ages of our executive officers as of March 1, 2014:

Executive Officers

Tuan Ha-Ngoc	61	Chief Executive Officer, President and Director and Acting Chief Financial Officer
William Slichenmyer	56	Chief Medical Officer
Michael P. Bailey	48	Chief Business Officer
Jeno Gyuris	54	Chief Scientific Officer
Joseph Vittiglio	42	Senior Vice President, General Counsel

Tuan Ha-Ngoc has served as President and Chief Executive Officer of our company and as a member of our Board of Directors since June 2002, and Acting Chief Financial Officer since December 2013. From 1999 to 2002, he was co-founder, President and Chief Executive Officer of deNovis, Inc., an enterprise-scale software development company for the automation of healthcare administrative functions. From 1998 to 1999, Mr. Ha-Ngoc was Corporate Vice President of Strategic Development for Wyeth, following Wyeth s acquisition of Genetics Institute, where Mr. Ha-Ngoc served as Executive Vice President with responsibility for corporate development, commercial operations and European and Japanese operations. Mr. Ha-Ngoc serves on the boards of a number of academic and nonprofit organizations, including the Harvard School of Dental Medicine, the Tufts School of Medicine, the MIT Koch Institute of Integrative Cancer Research and the Biomedical Sciences Career Program. Mr. Ha-Ngoc served on the Board of Directors of ArQule, Inc., from 2002 until 2006, and Human Genome Sciences, Inc. (now part of GlaxoSmithKline) from 2006 until 2012. He holds an M.B.A. from INSEAD and an M.A. in pharmacy from the University of Paris, France.

William Slichenmyer has served as our Chief Medical Officer since September 2009. Prior to joining our company, Dr. Slichenmyer served as Chief Medical Officer at Merrimack Pharmaceuticals from 2007 to September 2009. From 2000 to 2007, Dr. Slichenmyer worked at Pfizer Inc. in roles that included Vice President and Global Head of Oncology Clinical Development as well as positions in medical affairs and regulatory affairs. Dr. Slichenmyer holds a B.A. and M.D. from Case Western Reserve University and an Sc.M. in clinical investigation from Johns Hopkins University. Dr. Slichenmyer intends to leave the Company effective as of April 30, 2014.

Michael P. Bailey has served as our Chief Business Officer since June 2013. Mr. Bailey joined our company in September 2010 and served as our Chief Commercial Officer until June 2013. Prior to joining our company, Mr. Bailey served as Senior Vice President, Business Development and Chief Commercial Officer at Synta Pharmaceuticals from 2008 to September 2010. From 1999 to 2008, Mr. Bailey worked at ImClone, leading their commercial organization, most recently as Senior Vice President of Commercial Operations. Prior to his role at ImClone, Mr. Bailey managed the cardiovascular development portfolio at Genentech, Inc. from 1997 to 1999. Mr. Bailey started his career in the pharmaceutical industry as part of Smith-Kline Beecham s Executive Marketing Development Program, where he held a variety of commercial roles from 1992 to 1997, including sales, strategic planning, and product management. Mr. Bailey received a B.S. in psychology from St. Lawrence University and an M.B.A. in international marketing from the University of Notre Dame Graduate School of Business.

Jeno Gyuris has served as our Chief Scientific Officer since February 2012 and oversees all our research activities. Dr. Gyuris joined our company in January 2003 and served as our Vice President, Molecular Technologies until January 2007, as our Senior Vice President, Drug Discovery from January 2007 to January 2010 and our Senior Vice President, Head of Research from January 2010 to January 2012. From 1993 to 2002, Dr. Gyuris worked at GPC Biotech AG, formerly Mitotix Inc., where he held positions of increasing responsibility, most recently Vice President of Molecular Technologies. Dr. Gyuris has received several research fellowships in Europe and the United States, and is the author of numerous patents and publications. Dr. Gyuris received his Ph.D. from University of Szeged, Szeged, Hungary.

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Joseph Vittiglio has served as our Senior Vice President, General Counsel since January 2013. Mr. Vittiglio joined AVEO in October 2007 and served as our Corporate Counsel until January 2010, as our Vice President, Corporate Counsel from January 2010 until January 2012 and our Vice President, Chief Corporate Counsel from January 2012 to January 2013. Mr. Vittiglio has over 15 years of experience in corporate and securities law, with a particular focus in the biotech and pharmaceutical industries. Prior to joining AVEO, Mr. Vittiglio was the director of corporate legal affairs of Oscient Pharmaceuticals from 2005 through 2007. From 1998 through 2005, Mr. Vittiglio was an attorney at the Boston law firm of Mintz, Levin, Cohn, Ferris, Glovsky and Popeo, P.C., where his practice focused principally in the life science and technology industries, working on collaborative arrangements, corporate partnering, registered public securities offerings, mergers and acquisitions and venture financings. Mr. Vittiglio serves on the Board of Directors of two nonprofit organizations, the Casa Monte Cassino in Boston and Lynnfield Youth Soccer. Mr. Vittiglio holds a degree in International Relations from Tufts University and graduated from Northeastern University School of Law in 1996.

Available Information

We file reports and other information with the SEC as required by the Securities Exchange Act of 1934, as amended, which we refer to as the Exchange Act. You can find, copy and inspect information we file at the SEC s public reference room, which is located at 100 F Street, N.E., Room 1580, Washington, DC 20549. Please call the SEC at 1-800-SEC-0330 for more information about the operation of the SEC s public reference room. You can review our electronically filed reports and other information that we file with the SEC on the SEC s web site at http://www.sec.gov.

We were incorporated under the laws of the State of Delaware on October 19, 2001 as GenPath Pharmaceuticals, Inc. and changed our name to AVEO Pharmaceuticals, Inc. on March 1, 2005. Our principal executive offices are located at 650 East Kendall Street, Cambridge, Massachusetts, 02142, and our telephone number is (617) 299-5000. Our Internet website is http://www.aveooncology.com. We make available free of charge through our website our annual report on Form 10-K, quarterly reports on Form 10-Q, current reports on Form 8-K and amendments to those reports filed or furnished pursuant to Sections 13(a) and 15(d) of the Exchange Act. We also make available, free of charge on our website, the reports filed with the SEC by our executive officers, directors and 10% stockholders pursuant to Section 16 under the Exchange Act. We make these reports available through our website as soon as reasonably practicable after we electronically file such reports with, or furnish such reports to, the SEC, or, in the case of Section 16 reports, as soon as reasonably practicable after copies of those filings are provided to us by the filing persons. In addition, we regularly use our website to post information regarding our business, product development programs and governance, and we encourage investors to use our website, particularly the information in the section entitled For Investors and For Media, as a source of information about us.

The foregoing references to our website are not intended to, nor shall they be deemed to, incorporate information on our website into this report by reference.

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Item 1A. Risk Factors

Our business is subject to numerous risks. We caution you that the following important factors, among others, could cause our actual results to differ materially from those expressed in forward-looking statements made by us or on our behalf in this Annual Report on Form 10-K and other filings with the SEC, press releases, communications with investors and oral statements. Any or all of our forward-looking statements in this Annual Report on Form 10-K and in any other public statements we make may turn out to be wrong. They can be affected by inaccurate assumptions we might make or by known or unknown risks and uncertainties. Many factors mentioned in the discussion below will be important in determining future results. Consequently, no forward-looking statement can be guaranteed. Actual future results may differ materially from those anticipated in our forward-looking statements. We undertake no obligation to update any forward-looking statements, whether as a result of new information, future events or otherwise. You are advised, however, to consult any further disclosure we make in our reports filed with the SEC.

Risks Related to Our Financial Position and Capital Requirements

We will require substantial additional financing to achieve our goals, and a failure to obtain this necessary capital when needed could force us to delay, limit, reduce or terminate our research, product development or commercialization efforts.

Since our inception, most of our resources have been dedicated to the discovery and preclinical and clinical development of our product candidates. We believe that we will continue to expend substantial resources for the foreseeable future developing our preclinical and clinical product candidates. These expenditures will include costs associated with research and development, conducting preclinical and clinical trials, obtaining regulatory approvals and products from third-party manufacturers, as well as marketing and selling any products approved for sale. In addition, other unanticipated costs may arise.

Identifying potential product candidates and conducting preclinical testing and clinical trials is a time-consuming, expensive and uncertain process that takes years to complete, and we may never generate the necessary data or results required to obtain marketing approval and achieve product sales. In addition, our product candidates, if approved, may not achieve commercial success. Our commercial revenues, if any, will be derived from sales of products that we do not expect to be commercially available for many years, if at all.

We believe that our existing cash, cash equivalents, and marketable securities will allow us to fund our operating plan into at least the fourth quarter of 2015.

Because of the numerous risks and uncertainties associated with research, development and commercialization of pharmaceutical products, we are unable to estimate the exact amounts of our working capital requirements. Our future capital requirements depend on many factors, including:

- the number and characteristics of the product candidates we pursue;
- the scope, progress, results and costs of researching and developing our product candidates, and conducting preclinical and clinical trials;
- our ability to establish and maintain strategic partnerships, licensing or other arrangements and the financial terms of such agreements;
- our ability to secure alternative leasing or subleasing arrangements for our underutilized office at 650 East Kendall Street in Cambridge, Massachusetts, and to achieve related cost savings with respect to our current lease obligation;
- the timing of, and the costs involved in, obtaining regulatory approvals for our product candidates;

the costs related to the winding down of the discontinued tivozanib clinical development programs;

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- the costs involved in preparing, filing, prosecuting, maintaining, defending and enforcing patent claims, including litigation costs and the outcome of such litigation;

- whether we realize the full amount of any projected cost savings associated with our strategic restructurings;

- the absence of any breach or event of default under our loan agreement with Hercules or under any other agreements with third parties;

- the outcome of lawsuits against us, including the current lawsuits described below under Part I, Item 3 Legal Proceedings;

- the cost of commercialization activities if any of our product candidates are approved for sale, including marketing, sales and distribution costs;

- the cost of manufacturing our product candidates and any products we successfully commercialize; and

- the timing, receipt and amount of sales of, or royalties on, our future products, if any.

In addition, it is possible that Hercules Technology II, L.P. and Hercules Technology III, L.P., affiliates of Hercules Technology Growth, which we refer to collectively as Hercules, could take the position that the adverse outcome relating to the development and commercialization of tivozanib for RCC, including the FDA informing us that it would not approve our NDA for tivozanib for the treatment of patients with advanced RCC, the related shareholder litigation described under Part I, Item 3 Legal Proceedings and Astellas decision to terminate its collaboration with us, collectively, constitute a material adverse change under our loan and security agreement with Hercules, under which we had $19.4 million in loans outstanding as of December 31, 2013, which could trigger a repayment of all principal and interest due under the loan, unless such event of default is waived by Hercules.

In connection with our June 2013 restructuring and related reduction in workforce, we are reevaluating our facilities requirements for our headquarters and laboratory space at 650 East Kendall Street in Cambridge, Massachusetts. Failure to secure alternative arrangements with respect to our lease commitments could have an adverse effect on our operating results or financial condition.

If our available cash and cash equivalents are insufficient to satisfy our liquidity requirements, or if we identify additional opportunities to do so, we may seek to sell additional equity or debt securities or obtain additional credit facilities. The sale of additional equity or convertible debt securities may result in additional dilution to our stockholders. If we raise additional funds through the issuance of debt securities or preferred stock or through additional credit facilities, these securities and/or the loans under credit facilities could provide for rights senior to those of our common stock and could contain covenants that would restrict our operations. We may require additional capital beyond our currently forecasted amounts. Additional funds may not be available when we need them, on terms that are acceptable to us, or at all. If adequate funds are not available to us on a timely basis, we may be required to:

- delay, limit, reduce or terminate preclinical studies, clinical trials or other research and development activities for one or more of our product candidates; and/or

- delay, limit, reduce or terminate our establishment of sales and marketing capabilities or other activities that may be necessary to commercialize our product candidates, if approved.

We anticipate that we will continue to incur significant operating costs for the foreseeable future. It is uncertain if we will ever attain profitability in the future, which would depress the market price of our common stock.

We have incurred net losses in all prior reporting periods, other than for the year ended December 31, 2011, including a net loss of $107.0 million during the twelve months ended December 31, 2013. As of December 31, 2013, we had an accumulated deficit of $427.3 million. To date, we have not commercialized any products or

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generated any revenues from the sale of products, and absent the realization of sufficient revenues from product sales, we may never attain profitability in the future. Our losses have resulted principally from costs incurred in our discovery and development activities. We anticipate that we will continue to incur significant operating costs over the next several years as we seek to develop our preclinical and clinical product candidates.

If we do not successfully develop and obtain regulatory approval for our existing and future pipeline product candidates and effectively manufacture, market and sell any product candidates that are approved, we may never generate product sales, and even if we do generate product sales, we may never achieve or sustain profitability on a quarterly or annual basis. Our failure to become and remain profitable would depress the market price of our common stock and could impair our ability to raise capital, expand our business, diversify our product offerings or continue our operations.

Raising additional capital may cause dilution to our existing stockholders, and the terms of additional capital may impose restrictions on our operations or require us to relinquish rights to our technologies or product candidates.

We are likely to seek additional capital through a combination of private and public equity offerings, debt financings, strategic partnerships and alliances and licensing arrangements. Even if we reach a point where we believe we have sufficient funds for our current or future operating plans, we may seek additional capital due to favorable market conditions or strategic considerations. To the extent that we raise additional capital through the sale of equity or convertible debt securities, stockholders will be diluted, and the terms of these new securities may include liquidation or other preferences that adversely affect stockholders rights. Debt financing, if available, may involve agreements that include covenants limiting or restricting our ability to take certain actions, such as incurring debt, making capital expenditures or declaring dividends. If we raise additional funds through strategic partnerships and alliances or licensing arrangements with third parties, we may have to relinquish valuable rights to our technologies or product candidates, or grant licenses on terms that are not favorable to us.

A substantial portion of our future revenues may be dependent upon our existing and future strategic partnerships.

Our success will depend in significant part on our ability to attract and maintain strategic partners and strategic relationships to support the development and commercialization of our product candidates. As part of our business strategy, we have historically entered, and expect to enter in the future, into strategic partnerships relating to the development and commercialization of product candidates. In these partnerships, we would expect our strategic partner to provide substantial funding, as well as significant capabilities in development, marketing and sales. We may not be successful in entering into any such partnerships on favorable terms, if at all. Even if we do succeed in securing such partnerships, we may not be able to maintain them if, for example, development or approval of a product candidate is delayed or sales of an approved drug are disappointing.

If any of our strategic partners were to terminate their agreements with us, fail to meet their obligations or otherwise decrease their level of efforts, allocation of resources or other commitments under these agreements with us, our future revenues could be negatively impacted and the development and commercialization of product candidates could be interrupted.

In addition, if some or any of the development, regulatory and commercial milestones are not achieved or if certain net sales thresholds are not achieved, as set forth in the respective agreements, we will not fully realize the expected economic benefits of these partnership agreements. Further, the achievement of certain of the milestones under our partnership agreements will depend on factors that are outside of our control and most milestones are not expected to be achieved for several years, if at all. Any failure to successfully maintain our strategic partnership agreements could materially and adversely affect our ability to generate revenues. For

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example, in February 2014, Astellas gave us notice of its exercise of its right to terminate our collaboration agreement, for strategic reasons, based on the clinical status of tivozanib. As a result, we will not realize any future revenues from our partnership with Astellas.

Furthermore, any delay in entering into strategic partnerships could delay the development and commercialization of our product candidates and reduce their competitiveness, even if they reach the market. Any such delay related to our strategic partnerships could adversely affect our business.

We and certain of our present and former officers and directors have been named as defendants in a consolidated class action lawsuit that could result in substantial costs and divert management s attention.

We, and certain of our present and former officers and directors, were named as defendants in a consolidated class action lawsuit initiated in 2013 that generally alleges that we and certain of our present and former officers and directors violated Sections 10(b) and/or 20(a) of the Securities Exchange Act of 1934 and Rule 10b-5 promulgated thereunder by making allegedly false and/or misleading statements concerning the phase 3 trial design and results for our TIVO-1 study in an effort to lead investors to believe that the drug would receive approval from the FDA. The complaints seek unspecified damages, interest, attorneys fees, and other costs. Additionally, we received a subpoena from the SEC requesting documents and information concerning tivozanib, including related communications with the FDA, investors and others. Moreover, a plaintiff has filed a derivative complaint allegedly on our behalf, naming us, as a nominal defendant and also naming as defendants present and former members of the our board of directors, alleging breach of fiduciary duty and abuse of control between January 2012 and May 2013 with respect to allegedly misleading statements and omissions regarding tivozanib. The derivative complaint seeks, among other relief, unspecified damages, costs and expenses, including attorneys fees, an order requiring us to implement certain corporate governance reforms, restitution from the defendants and such other relief as the court might find just and proper.

We intend to engage in a vigorous defense of these lawsuits and are fully cooperating with the SEC regarding its fact-finding inquiry. However, we are unable to predict the outcome of these matters at this time. Moreover, any conclusion of these matters in a manner adverse to us would have a material adverse effect on our financial condition and business. For example, we could incur substantial costs not covered by our directors and officers liability insurance, suffer a significant adverse impact on our reputation and divert management s attention and resources from other priorities, including the execution of business plans and strategies that are important to our ability to grow our business, any of which could have a material adverse effect on our business. In addition, any of these matters could require payments that are not covered by, or exceed the limits of, our available directors and officers liability insurance, which could have a material adverse effect on our operating results or financial condition.

Additional similar lawsuits might be filed. For example, we are aware of a potential plaintiff, a purported purchaser of the Company s common stock, seeking to file a derivative complaint allegedly on behalf of the Company, which would name as defendants the Company and present and former members of the Company s board of directors. We intend to vigorously defend this lawsuit, if filed. However, we unable to predict the outcome of this potential lawsuit at this time.

Our business is in the preclinical and early clinical testing stage, which may make it difficult for you to evaluate the success of our business to date and to assess our future viability.

All of our product candidates are in preclinical development and clinical testing. We have not yet demonstrated our ability to obtain marketing approvals, manufacture a commercial scale medicine, or arrange for a third party to do so on our behalf, or conduct sales and marketing activities necessary for successful commercialization. Typically, it takes about ten to 15 years to develop one new medicine from the time it is discovered to when it is available for treating patients. Consequently, any predictions you make about our future success or viability may not be as accurate as they could be if we had a longer operating history.

In addition, as preclinical and early clinical testing stage business, we may encounter unforeseen expenses, difficulties, complications, delays and other known and unknown factors. To be profitable, we will need to

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transition from a company with a research focus to a company capable of supporting commercial activities. We may not be successful in such a transition.

Risks Related to Development, Clinical Testing and Regulatory Approval of Our Drug Candidates

All of our product candidates are still in preclinical and clinical development. Preclinical testing and clinical trials of our product candidates may not be successful, or may not result in approval by the U.S. Food and Drug Administration. If we are unable to obtain marketing approval or commercialize our product candidates, or experience significant delays in doing so, our business will be materially harmed.

Development of our product candidates, all of which are still in preclinical and clinical development, is at an early stage and we may not successfully develop a drug candidate that becomes a commercially viable drug. Our ability to generate product revenues, which we do not expect for many years, if ever, will depend heavily on the successful development and eventual commercialization of our product candidates. This process can take many years to complete, requiring the expenditure of substantial resources with highly uncertain results and a high risk of failure. Moreover, positive data from preclinical studies and clinical trials of our product candidates may not be predictive of results in ongoing or subsequent preclinical studies and clinical trials and may not be predictive of success in gaining any regulatory or marketing approvals necessary for commercialization.

The regulatory process can vary substantially based upon a variety of factors, including the type, complexity and novelty of the product candidates involved. If any of our product candidates are not shown to be safe and effective in humans through clinical trials, we and/or our strategic partners will not be able to obtain regulatory approval for such product candidate, and the resulting delays in developing other product candidates and conducting related preclinical studies and clinical trials would have a material adverse effect on our business, financial condition and results of operations.

The success of our product candidates will depend on several factors, many of which are beyond our control, including the following:

- successful enrollment in, and completion of, clinical trials and preclinical studies;
- our ability to demonstrate to the satisfaction of the FDA, and equivalent foreign regulatory agencies, the safety, efficacy and clinically meaningful benefit of our product candidates through completed, ongoing and any future clinical and non-clinical trials;
- our ability to obtain additional funding when needed;
- our ability to maintain collaborations with our strategic partners;
- achieving and maintaining compliance with all regulatory requirements applicable to pharmaceutical products;
- the prevalence and severity of adverse side effects;
- the ability of our third-party manufacturers to manufacture clinical trial and commercial supplies and to develop, validate and maintain commercially viable manufacturing processes that are compliant with cGMP;
- the availability, relative cost, safety and efficacy of alternative and competing treatments;

acceptance of the product by patients, the medical community and third-party payors;

launching commercial sales of the product, whether alone or in collaboration with others; and

our ability to avoid third-party patent interference or patent infringement claims;

If we do not achieve one or more of these factors in a timely manner or at all, we could experience significant delays or an inability to successfully commercialize our product candidates, which would materially harm our business.

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Any failure or delay in completing clinical trials for our product candidates, or unfavorable results from such trials, may prevent us from obtaining regulatory approval or commercializing product candidates on a timely basis, or at all, which would require us to incur additional costs and delay receipt of any product revenue.

We cannot predict whether we will encounter problems with any of our planned clinical trials that will cause us or regulatory authorities to delay, suspend or terminate those clinical trials. The completion of clinical trials for product candidates may be delayed, suspended or terminated for many reasons, including:

- delays in patient enrollment, and variability in the number and types of patients available for clinical trials, or high drop-out rates of patients in our clinical trials;
- our inability to obtain additional funding when needed;
- delays or failure in reaching agreement on acceptable clinical trial contracts or clinical trial protocols with prospective sites;
- failure of our third-party contractors or our investigators to comply with regulatory requirements or otherwise meet their contractual obligations in a timely manner;
- delays or failure in obtaining the necessary approvals from regulators or institutional review boards in order to commence a clinical trial at a prospective trial site, or their suspension or termination of a clinical trial once commenced;
- our inability to manufacture or obtain from third parties materials sufficient to complete our preclinical studies and clinical trials;
- difficulty in maintaining contact with patients after treatment, resulting in incomplete data;
- poor effectiveness of our product candidates during clinical trials, including without limitation, a failure to meet study objectives or obtain the requisite level of statistical significance imposed by the FDA or other regulatory agencies;
- safety issues, including serious adverse events associated with our product candidates;
- governmental or regulatory delays and changes in regulatory requirements, policy and guidelines; or
- varying interpretations of data by the FDA and similar foreign regulatory agencies.

Clinical trials often require the enrollment of large numbers of patients, and suitable patients may be difficult to identify and recruit. Our ability to enroll sufficient numbers of patients in our clinical trials depends on many factors, including the size of the patient population, the nature of the protocol, the proximity of patients to clinical sites, the eligibility criteria for the trial, competing clinical trials, the availability of approved effective drugs and the perception of the efficacy and safety of our product candidates. We may experience delays or difficulties in enrolling patients in our current and planned trials. If we fail to enroll and maintain the number of patients for which the clinical trial was designed, the statistical power of that clinical trial may be reduced which would make it harder to demonstrate that the product candidate being tested in such clinical trial is safe and effective. Additionally, we may not be able to enroll a sufficient number of qualified patients in a timely or cost-effective manner.

We, the FDA, other applicable regulatory authorities or institutional review boards may suspend or terminate clinical trials of a product candidate at any time if we or they believe the patients participating in such clinical trials are being exposed to unacceptable health risks or for other reasons.

Significant clinical trial delays could allow our competitors to obtain marketing approval before we do or shorten the patent protection period during which we may have the exclusive right to commercialize our product candidates. Our product development costs also will increase if we experience delays in completing clinical trials. In addition, it is impossible to predict whether legislative changes will be enacted, or whether FDA regulations, guidance or interpretations will be changed, or what the impact of such changes, if any, may be. If we experience any such problems, we may not have the financial resources to continue development of the product candidate that is affected or the development of any of our other product candidates.

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If we are not successful in discovering, developing and commercializing additional product candidates, our ability to expand our business and achieve our strategic objectives would be impaired.

A key element of our strategy is to discover, develop and commercialize novel antibody-based products. We are seeking to do so through our internal research programs and intend to explore strategic partnerships for such development. Research programs to identify product candidates require substantial technical, financial and human resources, whether or not any product candidates are ultimately identified. Our research programs may initially show promise in identifying potential product candidates, yet may fail to yield product candidates for clinical development for many reasons, including the following:

- the research methodology used may not be successful in identifying potential product candidates;
- competitors may develop alternatives that render our product candidates obsolete;
- a product candidate may upon further study be shown to have harmful side effects or other characteristics that indicate it is unlikely to be effective or otherwise does not meet applicable regulatory criteria;
- a product candidate may not be capable of being produced in commercial quantities at an acceptable cost, or at all; and
- a product candidate may not be accepted as safe and effective by patients, the medical community or third-party payors.

Even if we receive regulatory approval for any of our product candidates, we will be subject to ongoing FDA requirements and continued regulatory review, which may result in significant additional expense. Additionally, our product candidates, if approved, could be subject to labeling and other restrictions, post-approval requirements and market withdrawal and we may be subject to penalties if we fail to comply with regulatory requirements or experience unanticipated problems with our products.

Any regulatory approvals that we or our strategic partners receive for our product candidates may also be subject to limitations on the approved indicated uses for which the product may be marketed or to the conditions of approval, or contain requirements for potentially costly post-marketing requirements and testing, including post-approval clinical trials, surveillance to monitor the safety and efficacy of the product candidate, and implementation of a risk evaluation and mitigation strategy. In addition, if the FDA approves any of our product candidates, the manufacturing processes, labeling, packaging, distribution, adverse event reporting, storage, advertising, promotion and recordkeeping for the product will be subject to extensive and ongoing regulatory requirements. These requirements include submissions of safety and other post-marketing information and reports, registration, as well as continued compliance with cGMP and good clinical practices, or GCP, for any clinical trials that we conduct post-approval. Later discovery of previously unknown problems with a product, including adverse events of unanticipated severity or frequency, or with our third-party manufacturers or manufacturing processes, or failure to comply with regulatory requirements, may result in, among other things:

- restrictions on the marketing or manufacturing of the product, withdrawal of the product from the market, or voluntary or mandatory product recalls;
- fines, warning letters or holds on clinical trials;
- refusal by the FDA to approve pending applications or supplements to approved applications filed by us or our strategic partners, or suspension or revocation of product license approvals;

product seizure or detention, or refusal to permit the import or export of products; and

injunctions or the imposition of civil or criminal penalties.

The FDA s policies may change and additional government regulations may be enacted that could prevent, limit or delay regulatory approval of our product candidates. We cannot predict the likelihood, nature or extent of

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government regulation that may arise from future legislation or administrative action, either in the United States or abroad. If we are slow or unable to adapt to changes in existing requirements or the adoption of new requirements or policies, or if we are not able to maintain regulatory compliance, we may lose any marketing approval that we may have obtained and we may not achieve or sustain profitability, which would adversely affect our business.

Failure to obtain regulatory approval in jurisdictions outside the United States will prevent us from marketing our products abroad.

We intend to market our products, if approved, in international markets, which will require separate regulatory approvals and compliance with numerous and varying regulatory requirements. The approval procedures vary among countries and may involve requirements for additional testing, and the time required to obtain approval may differ from that required to obtain FDA approval. In addition, in many countries outside the United States, a product candidate must be approved for reimbursement before it can be approved for sale in that country. In some cases, the price that we intend to charge for our product is also subject to approval. Approval by the FDA does not ensure approval by regulatory authorities in other countries or jurisdictions, and approval by one foreign regulatory authority does not ensure approval by regulatory authorities in other foreign countries or jurisdictions or by the FDA. The foreign regulatory approval process may include all of the risks associated with obtaining FDA approval. We may not obtain foreign regulatory approvals on a timely basis, if at all. We and our strategic partners may not be able to file for regulatory approvals and may not receive necessary approvals to commercialize our products in any market.

If we are unable to successfully develop companion diagnostics for certain of our therapeutic product candidates, or experience significant delays in doing so, we may not realize the full commercial potential of these therapeutics.

A component of our business strategy may be to develop companion diagnostics for some of our therapeutic product candidates. There has been limited success to date industry-wide in developing companion diagnostics. To be successful, we will need to address a number of scientific, technical, regulatory and logistical challenges. We have limited experience in the development of diagnostics and may not be successful in developing appropriate diagnostics to pair with any of our therapeutic product candidates that receive marketing approval. The FDA and similar regulatory authorities outside the United States are generally expected to regulate companion diagnostics as medical devices. In each case, companion diagnostics require separate regulatory approval prior to commercialization. Given our limited experience in developing diagnostics, we expect to rely in part on third parties for their design, development and manufacture. If we, or any third parties that we engage to assist us, are unable to successfully develop companion diagnostics for our therapeutic product candidates, or experience delays in doing so, the development of our therapeutic product candidates may be adversely affected, our therapeutic product candidates may not receive marketing approval and we may not realize the full commercial potential of any therapeutics that receive marketing approval. As a result, our business would be harmed, possibly materially.

Risks Related to Our Business and Industry

We face substantial competition, which may result in others discovering, developing or commercializing products before, or more successfully, than we do.

Our future success depends on our ability to demonstrate and maintain a competitive advantage with respect to the design, development and commercialization of product candidates. Our objective is to design, develop and commercialize new products with superior efficacy, convenience, tolerability and safety. We expect any product candidate that we commercialize with our strategic partners or on our own will compete with existing, market-leading products.

Many of our potential competitors have substantially greater financial, technical and personnel resources than we have and several are already marketing products to treat the same indications, and having the same

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biological targets, as the product candidates we are developing, including with respect to cachexia. In addition, many of these competitors have significantly greater commercial infrastructures than we have. We will not be able to compete successfully unless we effectively:

- design and develop products that are superior to other products in the market in terms of, among other things, both safety and efficacy;
- attract qualified scientific, medical, sales and marketing and commercial personnel;
- obtain patent and/or other proprietary protection for our processes and product candidates;
- obtain required regulatory approvals;
- obtain favorable reimbursement, formulary and guideline status; and
- collaborate with others in the design, development and commercialization of new products.

Established competitors may invest heavily to quickly discover and develop novel compounds that could make our product candidates obsolete. In addition, any new product that competes with an approved product must demonstrate compelling advantages in efficacy, convenience, tolerability and safety in order to obtain approval, to overcome price competition and to be commercially successful. If we are not able to compete effectively against our current and future competitors, our business will not grow and our financial condition and operations will suffer.

We may not achieve research, development and commercialization goals in the time frames that we publicly estimate, which could have an adverse impact on our business and could cause our stock price to decline.

We set goals, and make public statements regarding our expected timing for certain accomplishments, such as the commencement and completion of preclinical studies, initiation and completion of clinical trials, filing and approval of regulatory applications for our product candidates and other developments and milestones under our research and development programs. The actual timing of these events can vary significantly due to a number of factors, including, without limitation, delays or failures in our and our current and potential future collaborators preclinical studies or clinical trials, the amount of time, effort and resources committed to our programs by us and our current and potential future collaborators and the uncertainties inherent in the regulatory approval process. As a result, there can be no assurance that our or our current and potential future collaborators preclinical studies and clinical trials will advance or be completed in the time frames we expect or announce, that we or our current and potential future collaborators will make regulatory submissions or receive regulatory approvals as planned or that we or our current and potential future collaborators will be able to adhere to our current schedule for the achievement of key milestones under any of our programs. If we or any collaborators fail to achieve one or more of the milestones described above as planned, our business could be materially adversely affected and the price of our common stock could decline.

Because we have limited experience in developing and commercializing pharmaceutical products, there is a limited amount of information about us upon which you can evaluate our business and prospects.

Although certain of our individual employees may have extensive experience in developing and commercializing pharmaceutical products, as an organization we have limited experience in developing and commercializing pharmaceutical products and have not yet demonstrated an ability to successfully overcome many of the risks and uncertainties frequently encountered by companies in new and rapidly evolving fields, particularly in the biopharmaceutical area. For example, to execute our business plan, we will need to successfully:

- execute product development activities;

obtain required regulatory approvals for the development and commercialization of our product candidates;

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build and maintain a strong intellectual property portfolio;

build and maintain robust sales, distribution, reimbursement and marketing capabilities;

obtain reimbursement and gain market acceptance for our products;

develop and maintain successful strategic relationships and partnerships; and

manage our spending as costs and expenses increase due to clinical trials, regulatory approvals and commercialization.

If we are unsuccessful in accomplishing these objectives, we may not be able to develop product candidates, raise capital, expand our business or continue our operations.

If we fail to attract and keep senior management and key scientific personnel, we may be unable to successfully develop our product candidates, conduct our clinical trials and commercialize our product candidates.

Our success depends in part on our continued ability to attract, retain and motivate highly qualified management, clinical and scientific personnel. We are highly dependent upon our senior management, as well as others on our management team. The loss of services of any of these individuals or one or more of our other members of management could delay or prevent the successful development of our product pipeline, the completion of our planned clinical trials or the commercialization of our product candidates. We do not carry key person insurance covering any members of our senior management. Our employment arrangements with all of these individuals are at will, meaning they or we can terminate their service at any time.

We face intense competition for qualified individuals from numerous pharmaceutical and biotechnology companies, universities, governmental entities and other research institutions, many of which have substantially greater resources with which to reward qualified individuals than we do. We may face challenges in retaining our existing senior management and key employees and recruiting new employees to join our company as our business needs change. We may be unable to attract and retain suitably qualified individuals, and our failure to do so could have an adverse effect on our ability to implement our future business plans.

Our employees may engage in misconduct or other improper activities, including noncompliance with regulatory standards and requirements and insider trading.

We are exposed to the risk of employee fraud or other misconduct. Misconduct by employees could include intentional failures to comply with FDA regulations, to provide accurate information to the FDA, to comply with manufacturing standards we have established, to comply with federal and state health-care fraud and abuse laws and regulations, to report financial information or data accurately or to disclose unauthorized activities to us. In particular, sales, marketing and business arrangements in the healthcare industry are subject to extensive laws and regulations intended to prevent fraud, kickbacks, self-dealing and other abusive practices. These laws and regulations may restrict or prohibit a wide range of pricing, discounting, marketing and promotion, sales commission, customer incentive programs and other business arrangements. Employee misconduct could also involve the improper use of information obtained in the course of clinical trials, which could result in regulatory sanctions and serious harm to our reputation. We have adopted a code of business conduct and ethics, but it is not always possible to identify and deter employee misconduct, and the precautions we take to detect and prevent this activity may not be effective in controlling unknown or unmanaged risks or losses or in protecting us from governmental investigations or other actions or lawsuits stemming from a failure to be in compliance with such laws or regulations. If any such actions are instituted against us, and we are not successful in defending ourselves or asserting our rights, those actions could have a significant impact on our business, including the imposition of significant fines or other sanctions.

In addition, during the course of our operations, our directors, executives and employees may have access to material, nonpublic information regarding our business, our results of operations or potential transactions we are

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considering. Despite the adoption of an Insider Trading Policy, we may not be able to prevent a director, executive or employee from trading in our common stock on the basis of, or while having access to, material, nonpublic information. If a director, executive or employee was to be investigated, or an action was to be brought against a director, executive or employee for insider trading, it could have a negative impact on our reputation and our stock price. Such a claim, with or without merit, could also result in substantial expenditures of time and money, and divert attention of our management team from other tasks important to the success of our business.

We may encounter difficulties in managing our growth and expanding our operations successfully.

As we seek to advance our product candidates through clinical trials and commercialization, we may need to expand our development, regulatory, manufacturing, marketing and sales capabilities or contract with third parties to provide these capabilities for us. Our future financial performance and our ability to commercialize our product candidates and to compete effectively will depend, in part, on our ability to manage any future growth effectively. To that end, we must be able to manage our development efforts and clinical trials effectively and hire, train and integrate additional management, administrative and sales and marketing personnel. We may not be able to accomplish these tasks, and our failure to accomplish any of them could prevent us from successfully growing our company.

If product liability lawsuits are brought against us, we may incur substantial liabilities and may be required to limit commercialization of our product candidates.

We face an inherent risk of product liability as a result of the clinical testing of our product candidates and will face an even greater risk if we commercialize any products. For example, we may be sued if any product we develop allegedly causes injury or is found to be otherwise unsuitable during product testing, manufacturing, marketing or sale. Any such product liability claims may include allegations of defects in manufacturing, defects in design, a failure to warn of dangers inherent in the product, negligence, strict liability, and a breach of warranties. Claims could also be asserted under state consumer protection acts. If we cannot successfully defend ourselves against product liability claims, we may incur substantial liabilities or be required to limit commercialization of our product candidates. Even successful defense could require significant financial and management resources. Regardless of the merits or eventual outcome, product liability claims may result in:

decreased demand for our product candidates or products that we may develop;

injury to our reputation;

withdrawal of clinical trial participants;

costs to defend the related litigation;

diversion of management s time and our resources;

substantial monetary awards to trial participants or patients;

product recalls, withdrawals or labeling, marketing or promotional restrictions;

loss of revenue;

the inability to commercialize our product candidates; and

a decline in our stock price.

Our inability to obtain and retain sufficient product liability insurance at an acceptable cost to protect against potential product liability claims could prevent or inhibit the commercialization of products we develop. We currently carry product liability insurance covering our clinical studies in the amount of $20 million in the aggregate. Although we maintain such insurance, any claim that may be brought against us could result in a court judgment or settlement in an amount that is not covered, in whole or in part, by our insurance or that is in excess of the limits of our insurance coverage. Our insurance policies also have various exclusions, and we may be

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subject to a product liability claim for which we have no coverage. We will have to pay any amounts awarded by a court or negotiated in a settlement that exceed our coverage limitations or that are not covered by our insurance, and we may not have, or be able to obtain, sufficient capital to pay such amounts.

We may incur significant costs complying with environmental laws and regulations, and failure to comply with these laws and regulations could expose us to significant liabilities.

We use hazardous chemicals and radioactive and biological materials in certain aspects of our business and are subject to a variety of federal, state and local laws and regulations governing the use, generation, manufacture, distribution, storage, handling, treatment and disposal of these materials. Although we believe our safety procedures for handling and disposing of these materials and waste products comply with these laws and regulations, we cannot eliminate the risk of accidental injury or contamination from the use, manufacture, distribution, storage, handling, treatment or disposal of hazardous materials. In the event of contamination or injury, or failure to comply with environmental, occupational health and safety and export control laws and regulations, we could be held liable for any resulting damages and any such liability could exceed our assets and resources. We do not maintain insurance for any environmental liability or toxic tort claims that may be asserted against us.

Risks Related to Commercialization of Our Product Candidates

We have limited sales, marketing, reimbursement and distribution experience and we will have to invest significant resources to develop those capabilities.

We have limited sales, marketing, reimbursement and distribution experience. To develop these capabilities, we will have to invest significant amounts of financial and management resources, some of which will be committed prior to any confirmation that any of our product candidates will be approved for commercial sale. We could face a number of additional risks in developing our commercial infrastructure, including:

- we may not be able to attract and build an effective marketing or sales force;
- the cost of establishing a marketing or sales force may not be justifiable in light of the revenues generated by any particular product; and
- our direct sales and marketing efforts may not be successful.

Furthermore, we may elect in the future to utilize strategic partners or contract sales forces to assist in the commercialization of other products, if approved. We may have limited or no control over the sales, marketing and distribution activities of these third parties. Our future revenues may depend heavily on the success of the efforts of these third parties.

Our commercial success depends upon attaining significant market acceptance of our product candidates, if approved, including among physicians, patients, healthcare payors and, in the cancer market, acceptance by the major operators of cancer clinics.

Even if one of our product candidates obtains regulatory approval, the product may not gain market acceptance among physicians, healthcare payors, patients and the medical community. Market acceptance of any products for which we receive approval depends on a number of factors, including:

- the efficacy and safety of the product candidate, as demonstrated in clinical trials;
- the clinical indications for which the drug is approved;

acceptance by physicians, major operators of cancer clinics, healthcare payors, physician networks and patients of the drug as a safe and effective treatment;

the potential and perceived advantages over alternative treatments;

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the cost of treatment in relation to alternative treatments;

the availability of adequate reimbursement and pricing by third parties and government authorities;

the continued projected growth of oncology drug markets;

relative convenience and ease of administration;

the prevalence and severity of adverse side effects; and

the effectiveness of our sales and marketing efforts.

If our approved drugs fail to achieve market acceptance, we would not be able to generate significant revenue.

Reimbursement may be limited or unavailable in certain market segments for our product candidates, which could make it difficult for us to sell any approved products profitably.

Market acceptance and sales of our product candidates will depend significantly on the availability of adequate coverage and reimbursement from third-party payors for any of our product candidates and may be affected by existing and future healthcare reform measures. Government authorities and third-party payors, such as private health insurers and health maintenance organizations, decide which drugs they will pay for and establish reimbursement levels. Reimbursement by a third-party payor may depend upon a number of factors, including the third-party payor s determination that use of a product is:

a covered benefit under its health plan;

safe, effective and medically necessary;

appropriate for the specific patient;

cost-effective; and

neither experimental nor investigational.

Obtaining coverage and reimbursement approval for a product from a government or other third-party payor is a time-consuming and costly process that could require us to provide supporting scientific, clinical and cost-effectiveness data for the use of our products to the payor. We may not be able to provide data sufficient to gain acceptance with respect to coverage and reimbursement. We cannot be sure that coverage or adequate reimbursement will be available for any of our product candidates. Also, we cannot be sure that reimbursement amounts will not reduce the demand for, or the price of, our products. If reimbursement is not available or is available only to limited levels, we may not be able to commercialize certain of our products.

In both the United States and certain foreign jurisdictions, there have been a number of legislative and regulatory changes to the healthcare system that could impact our ability to sell our products profitably. In particular, the Medicare Modernization Act of 2003 revised the payment methodology for many products under Medicare. This has resulted in lower rates of reimbursement. There have been numerous other federal and state initiatives designed to reduce payment for pharmaceuticals.

As a result of legislative proposals and the trend towards managed healthcare in the United States, third-party payors are increasingly attempting to contain healthcare costs by limiting both coverage and the level of reimbursement of new drugs. They may also refuse to provide any coverage of approved products for medical indications other than those for which the FDA has granted market approvals. As a result, significant uncertainty exists as to whether and how much third-party payors will reimburse patients for their use of newly approved drugs, which in turn will put pressure on the pricing of drugs. We expect to experience pricing pressures in connection with the sale of any products we may develop or commercialize due to the trend toward managed healthcare, the increasing influence of health maintenance organizations, additional legislative proposals, as well

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as country, regional, or local healthcare budget limitations. Any products that we may develop or commercialize may not be considered cost-effective, and coverage and reimbursement may not be available or sufficient to allow us to sell our products on a profitable basis.

Foreign governments may impose price controls, which may adversely affect our future profitability.

We and our strategic partners intend to seek approval to market our future products in both the United States and in foreign jurisdictions. If approval is obtained in one or more foreign jurisdictions, we and our strategic partners will be subject to rules and regulations in those jurisdictions relating to our product. In some foreign countries, particularly in countries in the European Union, the pricing of prescription pharmaceuticals and biologics is subject to governmental control. In these countries, pricing negotiations with governmental authorities can take considerable time after the receipt of marketing approval for a product candidate. If reimbursement of our future products is unavailable or limited in scope or amount, or if pricing is set at unsatisfactory levels, we may be unable to achieve or sustain profitability.

Healthcare reform measures could hinder or prevent our product candidates commercial success.

The U.S. government and other governments have shown significant interest in pursuing healthcare reform. Any government-adopted reform measures could adversely impact the pricing of healthcare products and services in the U.S. or internationally and the amount of reimbursement available from governmental agencies or other third-party payors. The continuing efforts of the U.S. and foreign governments, insurance companies, managed care organizations and other payors of healthcare services to contain or reduce healthcare costs may adversely affect our ability to set prices which we believe are fair for any products we may develop and commercialize, and our ability to generate revenues and achieve and maintain profitability.

New laws, regulations and judicial decisions, or new interpretations of existing laws, regulations and decisions, that relate to healthcare availability, methods of delivery or payment for products and services, or sales, marketing or pricing, may limit our potential revenue, and we may need to revise our research and development programs. The pricing and reimbursement environment may change in the future and become more challenging due to several reasons, including policies advanced by the U.S. government, new healthcare legislation or fiscal challenges faced by government health administration authorities. Specifically, in both the U.S. and some foreign jurisdictions, there have been a number of legislative and regulatory proposals and initiatives to change the healthcare system in ways that could affect our ability to sell any products we may develop and commercialize profitably. Some of these proposed and implemented reforms could result in reduced reimbursement rates for our potential products, which would adversely affect our business strategy, operations and financial results.

For example, in March 2010, President Obama signed into law a legislative overhaul of the U.S. healthcare system, known as the Patient Protection and Affordable Care Act of 2010, as amended by the Healthcare and Education Affordability Reconciliation Act of 2010, or the PPACA, which may have far reaching consequences for life science companies like us. As a result of this legislation, substantial changes could be made to the current system for paying for healthcare in the United States, including changes made in order to extend medical benefits to those who currently lack insurance coverage. Extending coverage to a large population could substantially change the structure of the health insurance system and the methodology for reimbursing medical services, drugs and devices. These structural changes could entail modifications to the existing system of private payors and government programs, such as Medicare and Medicaid, creation of a government-sponsored healthcare insurance source, or some combination of both, as well as other changes. Restructuring the coverage of medical care in the United States could impact the reimbursement for prescribed drugs, biopharmaceuticals, medical devices, or our product candidates. If reimbursement for our approved product candidates, if any, is substantially less that we expect in the future, or rebate obligations associated with them are substantially increased, our business could be materially and adversely impacted.

Further federal and state proposals and healthcare reforms could limit the prices that can be charged for the product candidates that we develop and may further limit our commercial opportunity. Our results of operations

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could be materially adversely affected by the PPACA, by Medicare prescription drug coverage legislation, by the possible effect of such current or future legislation on amounts that private insurers will pay and by other healthcare reforms that may be enacted or adopted in the future.

Risks Related to Our Dependence on Third Parties

We may not be successful in establishing and maintaining additional strategic partnerships, which could adversely affect our ability to develop and commercialize products.

In addition to our current strategic partnerships, a part of our strategy is to enter into additional strategic partnerships in the future, including alliances with major biotechnology or pharmaceutical companies. We face significant competition in seeking appropriate strategic partners and the negotiation process is time-consuming and complex. Moreover, we may not be successful in our efforts to establish a strategic partnership or other alternative arrangements for any product candidates and programs because our research and development pipeline may be insufficient, our product candidates and programs may be deemed to be at too early of a stage of development for collaborative effort and/or third parties may not view our product candidates and programs as having the requisite potential to demonstrate safety and efficacy. Even if we are successful in our efforts to establish new strategic partnerships, the terms that we agree upon may not be favorable to us and we may not be able to maintain such strategic partnerships if, for example, development or approval of a product candidate is delayed or sales of an approved product are disappointing. Any delay in entering into new strategic partnership agreements related to our product candidates could have an adverse effect on our business or our operating plan, including delaying the development and commercialization of our product candidates.

Moreover, if we fail to establish and maintain additional strategic partnerships related to our product candidates:

- the development of certain of our current or future product candidates may be terminated or delayed;
- our cash expenditures related to development of certain of our current or future product candidates would increase significantly and we may need to seek additional financing;
- we may be required to hire additional employees or otherwise develop expertise, such as sales and marketing expertise, for which we have not budgeted; and
- we will bear all of the risk related to the development of any such product candidates.

In addition, if we fail to establish and maintain additional strategic partnerships involving our Human Response Platform, we would not realize its potential as a means of identifying and validating targets for new cancer therapies in collaboration with strategic partners or of identifying biomarkers to aid in the development of our strategic partners drug candidates.

If any of our current or future strategic partners fails to perform its obligations or terminates its agreement with us, the development and commercialization of the product candidates under such agreement could be delayed or terminated and our business could be substantially harmed.

As part of our business strategy, we plan to enter into strategic partnerships in the future. If any current or future strategic partners do not devote sufficient time and resources to its arrangements with us, we may not realize the potential commercial benefits of the arrangement, and our results of operations may be adversely affected. In addition, if any strategic partner were to breach or terminate its arrangements with us, the development and commercialization of the affected product candidate could be delayed, curtailed or terminated because we may not have sufficient financial resources or capabilities to continue development and commercialization of the product candidate on its own, and we may find it difficult to attract a new alliance partner for such product candidate.

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Much of the potential revenue from any strategic partnership we may enter into in the future will likely consist of contingent payments, such as royalties payable on sales of any successfully developed drugs. Any such contingent revenue will depend upon our, and our strategic partner s ability to successfully develop, introduce, market and sell new drugs. In some cases, we will not be involved in these processes, and we will depend entirely on our strategic partners. Any of our future strategic partners may fail to develop or effectively commercialize these drugs because it:

- decides not to devote the necessary resources because of internal constraints, such as limited personnel with the requisite scientific expertise, limited cash resources or specialized equipment limitations, or the belief that other product candidates may have a higher likelihood of obtaining regulatory approval or may potentially generate a greater return on investment;
- does not have sufficient resources necessary to carry the product candidate through clinical development, regulatory approval and commercialization; or
- cannot obtain the necessary regulatory approvals.

If one or more of our strategic partners fails to develop or effectively commercialize product candidates for any of the foregoing reasons, we may not be able to replace the strategic partner with another partner to develop and commercialize a product candidate under the terms of the strategic partnership. We may also be unable to obtain, on terms acceptable to us, a license from such strategic partner to any of its intellectual property that may be necessary or useful for us to continue to develop and commercialize a product candidate. Any of these events could have a material adverse effect on our business, results of operations and our ability to achieve future profitability, and could cause our stock price to decline.

We rely on third-party manufacturers to produce our preclinical and clinical drug supplies and we intend to rely on third parties to produce commercial supplies of any approved product candidates. Any failure by a third-party manufacturer to produce supplies for us may delay or impair our ability to complete our clinical trials or commercialize our product candidates.

We have relied upon third-party manufacturers for the manufacture of our product candidates for preclinical and clinical testing purposes and intend to continue to do so in the future. If we are unable to arrange for third-party manufacturing sources, or to do so on commercially reasonable terms, we may not be able to complete development of such other product candidates or market them.

Reliance on third-party manufacturers entails risks to which we would not be subject if we manufactured product candidates ourselves, including reliance on the third party for regulatory compliance and quality assurance, the possibility of breach of the manufacturing agreement by the third party because of factors beyond our control (including a failure to synthesize and manufacture our product candidates in accordance with our product specifications), failure of the third party to accept orders for supply of drug substance or drug product and the possibility of termination or nonrenewal of the agreement by the third-party, based on its own business priorities, at a time that is costly or damaging to us. In addition, the FDA and other regulatory authorities require that our product candidates be manufactured according to cGMP and similar foreign standards. Any failure by our third-party manufacturers to comply with cGMP or failure to scale-up manufacturing processes as needed, including any failure to deliver sufficient quantities of product candidates in a timely manner, could lead to a delay in, or failure to obtain, regulatory approval of any of our product candidates. In addition, such failure could be the basis for action by the FDA to withdraw approvals for product candidates previously granted to us and for other regulatory action, including recall or seizure, fines, imposition of operating restrictions, total or partial suspension of production or injunctions.

We rely on our manufacturers to purchase from third-party suppliers the materials necessary to produce our product candidates for our clinical studies. There are a small number of suppliers for certain capital equipment and raw materials that we use to manufacture our drugs. Such suppliers may not sell this capital equipment or these raw materials to our manufacturers at the times we need them or on commercially reasonable terms. We do not have any control over the process or timing of the acquisition of this capital equipment or these raw materials by our

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manufacturers. Moreover, we currently do not have any agreements for the commercial production of these raw materials. Any significant delay in the supply of a product candidate or the raw material components thereof for an ongoing clinical trial due to the need to replace a third-party manufacturer could considerably delay completion of our clinical studies, product testing and potential regulatory approval of our product candidates. If our manufacturers or we are unable to purchase these raw materials after regulatory approval has been obtained for our product candidates, the commercial launch of our product candidates would be delayed or there would be a shortage in supply, which would impair our ability to generate revenues from the sale of our product candidates.

Because of the complex nature of many of our early stage compounds and product candidates, our manufacturers may not be able to manufacture such compounds and product candidates at a cost or in quantities or in a timely manner necessary to develop and commercialize related products. If we successfully commercialize any of our drugs, we may be required to establish or access large-scale commercial manufacturing capabilities. In addition, as our drug development pipeline increases and matures, we will have a greater need for clinical trial and commercial manufacturing capacity. We do not own or operate manufacturing facilities for the production of clinical or commercial quantities of our product candidates and we currently have no plans to build our own clinical or commercial scale manufacturing capabilities. To meet our projected needs for commercial manufacturing, third parties with whom we currently work will need to increase their scale of production or we will need to secure alternate suppliers.

We rely on third parties to conduct preclinical and clinical trials for our product candidates, and if they do not properly and successfully perform their obligations to us, we may not be able to obtain regulatory approvals for our product candidates.

We, in consultation with our strategic partners, design the clinical trials for our product candidates, but we rely on contract research organizations and other third parties to assist us in managing, monitoring and otherwise carrying out many of these trials. We compete with larger companies for the resources of these third parties.

Although we rely on these third parties to conduct many of our clinical trials, we are responsible for ensuring that each of our clinical trials is conducted in accordance with its general investigational plan and protocol. Moreover, the FDA and foreign regulatory agencies require us to comply with regulations and standards, commonly referred to as good clinical practices, for designing, conducting, monitoring, recording, analyzing, and reporting the results of clinical trials to assure that the data and results are credible and accurate and that the rights, integrity and confidentiality of trial participants are protected. Our reliance on third parties that we do not control does not relieve us of these responsibilities and requirements.

The third parties on whom we rely generally may terminate their engagements with us at any time. If we are required to enter into alternative arrangements because of any such termination, the introduction of our product candidates to market could be delayed.

If these third parties do not successfully carry out their duties under their agreements with us, if the quality or accuracy of the data they obtain is compromised due to their failure to adhere to our clinical trial protocols or regulatory requirements, or if they otherwise fail to comply with clinical trial protocols or meet expected deadlines, our clinical trials may not meet regulatory requirements. If our clinical trials do not meet regulatory requirements or if these third parties need to be replaced, our preclinical development activities or clinical trials may be extended, delayed, suspended or terminated. If any of these events occur, we may not be able to obtain regulatory approval of our product candidates and our reputation could be harmed.

Risks Related to Our Intellectual Property Rights

We could be unsuccessful in obtaining adequate patent protection for one or more of our product candidates.

We cannot be certain that patents will be issued or granted with respect to applications that are currently pending, or that issued or granted patents will not later be found to be invalid and/or unenforceable. The patent position of biotechnology and pharmaceutical companies is generally uncertain because it involves complex legal

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and factual considerations. The standards applied by the United States Patent and Trademark Office and foreign patent offices in granting patents are not always applied uniformly or predictably. For example, there is no uniform worldwide policy regarding patentable subject matter or the scope of claims allowable in biotechnology and pharmaceutical patents. Consequently, patents may not issue from our pending patent applications. As such, we do not know the degree of future protection that we will have on our proprietary products and technology. The scope of patent protection that the U.S. Patent and Trademark Office will grant with respect to the antibodies in our antibody product pipeline is uncertain. It is possible that the U.S. Patent and Trademark Office will not allow broad antibody claims that cover closely related antibodies as well as the specific antibody. Upon receipt of FDA approval, competitors would be free to market antibodies almost identical to ours, thereby decreasing our market share.

Issued patents covering one or more of our products could be found invalid or unenforceable if challenged in court.

If we or one of our corporate partners were to initiate legal proceedings against a third-party to enforce a patent covering one of our products, the defendant could counterclaim that our patent is invalid and/or unenforceable. In patent litigation in the United States, defendant counterclaims alleging invalidity and/or unenforceability are commonplace. Grounds for a validity challenge could be an alleged failure to meet any of several statutory requirements, for example, lack of novelty, obviousness or non-enablement. Grounds for an unenforceability assertion could be an allegation that someone connected with prosecution of the patent withheld relevant information from the U.S. Patent and Trademark Office, or made a misleading statement, during prosecution. Although we have conducted due diligence on patents we have exclusively in-licensed, and we believe that we have conducted our patent prosecution in accordance with the duty of candor and in good faith, the outcome following legal assertions of invalidity and unenforceability during patent litigation is unpredictable. With respect to the validity question, for example, we cannot be certain that there is no invalidating prior art, of which we and the patent examiner were unaware during prosecution. If a defendant were to prevail on a legal assertion of invalidity and/or unenforceability, we would lose at least part, and perhaps all, of the patent protection on one of our products or certain aspects of our Human Response Platform. Such a loss of patent protection could have a material adverse impact on our business.

Claims that our platform technologies, our products or the sale or use of our products infringe the patent rights of third parties could result in costly litigation or could require substantial time and money to resolve, even if litigation is avoided.

We cannot guarantee that our platform technologies, our products, or the use of our products, do not infringe third-party patents. Third parties might allege that we are infringing their patent rights or that we have misappropriated their trade secrets. Such third parties might resort to litigation against us. The basis of such litigation could be existing patents or patents that issue in the future.

It is also possible that we failed to identify relevant third-party patents or applications. For example, applications filed before November 29, 2000 and certain applications filed after that date that will not be filed outside the United States remain confidential until patents issue. Patent applications in the United States and elsewhere are published approximately 18 months after the earliest filing, which is referred to as the priority date. Therefore, patent applications covering our products or platform technology could have been filed by others without our knowledge. Additionally, pending patent applications which have been published can, subject to certain limitations, be later amended in a manner that could cover our platform technologies, our products or the use of our products.

With regard to tivozanib, we are aware of a third-party United States patent, and corresponding foreign counterparts, that contain broad claims related to use of an organic compound, that, among other things, inhibits the tyrosine phosphorylation of a VEGF receptor caused by VEGF binding to such VEGF receptor. Additionally, tivozanib falls within the scope of certain pending patent applications that have broad generic disclosure and

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disclosure of certain compounds possessing structural similarities to tivozanib. Although we believe it is unlikely that such applications will lead to issued claims that would cover tivozanib and still be valid in view of the prior art, patent prosecution is inherently unpredictable. We are also aware of third-party United States patents that contain broad claims related to the use of a tyrosine kinase inhibitor in combination with a DNA damaging agent such as chemotherapy or radiation and we have received written notice from the owners of such patents indicating that they believe we may need a license from them in order to avoid infringing their patents. With regard to ficlatuzumab, we are aware of two separate families of United States patents, United States patent applications and foreign counterparts, with each of the two families being owned by a different third-party, that contain broad claims related to anti-HGF antibodies having certain binding properties and their use. With regard to AV-203, we are aware of a third-party United States patent that contains broad claims relating to anti-ErbB3 antibodies. With regard to GDF-15, we are aware of a United States patent that contains claims related to antibodies binding to GDF-15 protein, which is set to expire in 2014. Based on our analyses, if any of the above third-party patents were asserted against us, we do not believe our proposed products or activities would be found to infringe any valid claim of these patents. If we were to challenge the validity of any issued United States patent in court, we would need to overcome a statutory presumption of validity that attaches to every United States patent. This means that in order to prevail, we would have to present clear and convincing evidence as to the invalidity of the patent s claims. There is no assurance that a court would find in our favor on questions of infringement or validity.

In order to avoid or settle potential claims with respect to any of the patent rights described above or any other patent rights of third parties, we may choose or be required to seek a license from a third-party and be required to pay license fees or royalties or both. These licenses may not be available on acceptable terms, or at all. Even if we or our strategic partners were able to obtain a license, the rights may be non-exclusive, which could result in our competitors gaining access to the same intellectual property. Ultimately, we could be prevented from commercializing a product, or be forced to cease some aspect of our business operations, if, as a result of actual or threatened patent infringement claims, we are unable to enter into licenses on acceptable terms. This could harm our business significantly.

Defending against claims of patent infringement or misappropriation of trade secrets could be costly and time-consuming, regardless of the outcome. Thus, even if we were to ultimately prevail, or to settle at an early stage, such litigation could burden us with substantial unanticipated costs. In addition, litigation or threatened litigation could result in significant demands on the time and attention of our management team, distracting them from the pursuit of other company business.

Unfavorable outcomes in intellectual property litigation could limit our research and development activities and/or our ability to commercialize certain products.

If third parties successfully assert intellectual property rights against us, we might be barred from using aspects of our technology platform, or barred from developing and commercializing related products. Prohibitions against using specified technologies, or prohibitions against commercializing specified products, could be imposed by a court or by a settlement agreement between us and a plaintiff. In addition, if we are unsuccessful in defending against allegations of patent infringement or misappropriation of trade secrets, we may be forced to pay substantial damage awards to the plaintiff. There is inevitable uncertainty in any litigation, including intellectual property litigation. There can be no assurance that we would prevail in any intellectual property litigation, even if the case against us is weak or flawed. If litigation leads to an outcome unfavorable to us, we may be required to obtain a license from the patent owner in order to continue our research and development programs or to market our product(s). It is possible that the necessary license will not be available to us on commercially acceptable terms, or at all. This could limit our research and development activities, our ability to commercialize specified products, or both.

Most of our competitors are larger than we are and have substantially greater resources. They are, therefore, likely to be able to sustain the costs of complex patent litigation longer than we could. In addition, the

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uncertainties associated with litigation could have a material adverse effect on our ability to raise the funds necessary to continue our clinical trials, continue our internal research programs, in-license needed technology, or enter into strategic partnerships that would help us bring our product candidates to market.

In addition, any future patent litigation, interference or other administrative proceedings will result in additional expense and distraction of our personnel. An adverse outcome in such litigation or proceedings may expose us or our strategic partners to loss of our proprietary position, expose us to significant liabilities, or require us to seek licenses that may not be available on commercially acceptable terms, if at all.

Intellectual property litigation may lead to unfavorable publicity that harms our reputation and causes the market price of our common stock to decline.

During the course of any patent litigation, there could be public announcements of the results of hearings, rulings on motions, and other interim proceedings in the litigation. If securities analysts or investors regard these announcements as negative, the perceived value of our products, programs, or intellectual property could be diminished. Accordingly, the market price of our common stock may decline.

Tivozanib and AV-380 are protected by patents exclusively licensed from other companies or institutions. If the licensors terminate the licenses or fail to maintain or enforce the underlying patents, our competitive position and our market share in the markets for any of our approved products will be harmed.

We are a party to several license agreements under which certain aspects of our business depend on patents and/or patent applications owned by other companies or institutions. In particular, we hold exclusive licenses from Kyowa Hakko Kirin for tivozanib, and from St. Vincent s Hospital Sydney, Australia, Limited for therapeutic applications that benefit from inhibition or decreased expression or activity of MIC-1, which we refer to as GDF-15 and which we are using in our AV-380 program. We are likely to enter into additional license agreements as part of the development of our business in the future. Our licensors may not successfully prosecute certain patent applications under which we are licensed and on which our business depends. Even if patents issue from these applications, our licensors may fail to maintain these patents, may decide not to pursue litigation against third-party infringers, may fail to prove infringement, or may fail to defend against counterclaims of patent invalidity or unenforceability. In addition, in spite of our best efforts, our licensors might conclude that we have materially breached our license agreements and might therefore terminate the license agreements, thereby removing our ability to obtain regulatory approval and to market products covered by these license agreements. If these in-licenses are terminated, or if the underlying patents fail to provide the intended market exclusivity, competitors would have the freedom to seek regulatory approval of, and to market, products identical to ours. This could have a material adverse effect on our competitive business position and our business prospects.

We could be unsuccessful in obtaining patent protection on one or more components of our technology platform.

We believe that an important factor in our competitive position relative to other companies in the field of targeted oncology therapeutics is our proprietary Human Response Platform. This platform is useful for identifying new targets for drug discovery, confirming that newly-identified drug targets actually play a role in cancer, testing new compounds for effectiveness as drugs, and identifying traits useful for predicting which patients will respond to which drugs. We own issued U.S. patents covering our chimeric model technology and directed complementation technology. However, patent protection on other aspects of our technology platform, such as our reconstituted human breast tumor model, is still pending. There is no guarantee that any of such pending patent applications, in the United States or elsewhere, will result in issued patents, and, even if patents eventually issue, there is no certainty that the claims in the eventual patents will have adequate scope to preserve our competitive position. Third parties might invent alternative technologies that would substitute for our technology platform while being outside the scope of the patents covering our platform technology. By successfully designing around our patented technology, third parties could substantially weaken our competitive position in oncology research and development.

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Confidentiality agreements with employees and third parties may not prevent unauthorized disclosure of trade secrets and other proprietary information.

In addition to patents, we rely on trade secrets, technical know-how, and proprietary information concerning our business strategy in order to protect our competitive position in the field of oncology. In the course of our research, development and business activities, we often rely on confidentiality agreements to protect our proprietary information. Such confidentiality agreements are used, for example, when we talk to vendors of laboratory or clinical development services or potential strategic partners. In addition, each of our employees is required to sign a confidentiality agreement upon joining our company. We take steps to protect our proprietary information, and we seek to carefully draft our confidentiality agreements to protect our proprietary interests. Nevertheless, there can be no guarantee that an employee or an outside party will not make an unauthorized disclosure of our proprietary confidential information. This might happen intentionally or inadvertently. It is possible that a competitor will make use of such information, and that our competitive position will be compromised, in spite of any legal action we might take against persons making such unauthorized disclosures.

Trade secrets are difficult to protect. Although we use reasonable efforts to protect our trade secrets, our employees, consultants, contractors, or outside scientific collaborators might intentionally or inadvertently disclose our trade secret information to competitors. Enforcing a claim that a third-party illegally obtained and is using any of our trade secrets is expensive and time-consuming, and the outcome is unpredictable. In addition, courts outside the United States sometimes are less willing than U.S. courts to protect trade secrets. Moreover, our competitors may independently develop equivalent knowledge, methods and know-how.

Our research and development strategic partners may have rights to publish data and other information to which we have rights. In addition, we sometimes engage individuals or entities to conduct research relevant to our business. The ability of these individuals or entities to publish or otherwise publicly disclose data and other information generated during the course of their research is subject to certain contractual limitations. These contractual provisions may be insufficient or inadequate to protect our confidential information. If we do not apply for patent protection prior to such publication, or if we cannot otherwise maintain the confidentiality of our proprietary technology and other confidenti