AVEO PHARMACEUTICALS INC
Form 10-K
March 22, 2017

UNITED STATES

SECURITIES AND EXCHANGE COMMISSION

Washington, D.C. 20549

FORM 10-K

(Mark One)

ANNUAL REPORT PURSUANT TO SECTION 13 OR 15(d) OF THE SECURITIES EXCHANGE ACT OF 1934
For the fiscal year ended: December 31, 2016

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.)

One Broadway, 14th Floor

Cambridge, Massachusetts 02142

(Address of Principal Executive Offices) (zip code)

Registrant’s telephone number, including area code: (617) 588-1960

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 Select 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

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

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

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

Indicate by check mark if disclosure of delinquent filers pursuant to Item 405 of Regulation S-K (§229.405) 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
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

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 Select Market at the close of business on June 30, 2016, was $61,056,258

The number of shares outstanding of the registrant's Common Stock as of March 17, 2017 were 75,862,946.

Documents incorporated by reference:

Portions of our definitive proxy statement for our 2017 annual meeting of stockholders are incorporated by reference into Part III of this Annual Report on Form 10-K.

AVEO PHARMACEUTICALS, INC.

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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

Any statement contained in this Annual Report on Form 10-K or in the documents we incorporate by reference herein other than a statement of historical fact, may be a forward-looking statement, including statements regarding our and our collaborators’ future discovery, development and commercialization efforts, our strategy, future operations, future financial position, future revenue, projected costs, prospects, plans and objectives of management. In some cases, you can identify forward-looking statements by such terms as “anticipate,” “believe,” “could,” “estimate,” “expect,” “forecast,” “in “may,” “plan,” “project,” “should,” “target,” “will,” “would” or other words that convey uncertainty of future events or outcom identify these forward-looking statements. Forward-looking statements may include, but are not limited to, statements about:

- the initiation, timing, progress and results of future clinical trials, and our development programs;
- our plans to develop and commercialize our product candidates;
- our ability to secure new collaborations, maintain existing collaborations or obtain additional funding;
- the timing or likelihood of regulatory filings and approvals;
- the implementation of our business model, strategic plans for our business, product candidates and technology;
- our commercialization, marketing and manufacturing capabilities and strategy;
- the rate and degree of market acceptance and clinical utility of our products;
- our competitive position;
- our intellectual property position;
- developments and projections relating to our competitors and our industry;
- our estimates of the period in which we anticipate that existing cash, cash equivalents and investments will enable us to fund our current and planned operations;
- our estimates regarding expenses, future revenue, capital requirements and needs for additional financing; and
- our ability to continue as a going concern.

Our actual results may differ materially from those indicated by these forward-looking statements as a result of various important factors, including risks relating to:

- our ability to maintain our third party collaboration agreements and our ability, and the ability of our licensees, to achieve development and commercialization objectives under these arrangements;
- our ability, and the ability of our licensees, to demonstrate to the satisfaction of applicable regulatory agencies the safety, efficacy and clinically meaningful benefit of our product candidates;
- our ability to successfully enroll and complete clinical trials of our product candidates, including our TIVO-3 trial;
- our ability to maintain compliance with the $10.0 million financial covenant under our loan agreement with Hercules;
- our ability to achieve and maintain compliance with all regulatory requirements applicable to our product candidates;
- our ability to obtain and maintain adequate protection for intellectual property rights relating to our product candidates and technologies;
- developments, expenses and outcomes related to our ongoing shareholder litigation;
- our ability to successfully implement our strategic plans;
- our ability to raise the substantial additional funds required to achieve our goals;
- unplanned capital requirements;
- adverse general economic and industry conditions;

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- competitive factors;
- our ability to continue as a going concern; and
- those risks discussed under the heading “Risk Factors” in Part I, Item 1A of this report.

If one or more of these factors materialize, or if any underlying assumptions prove incorrect, our actual results, performance or achievements may vary materially from any future results, performance or achievements expressed or implied by the forward-looking statements we make.

You should consider these factors and the other cautionary statements made in this report and the documents we incorporate by reference herein as being applicable to all related forward-looking statements wherever they appear in this report or the documents incorporated by reference. While we may elect to update forward-looking statements wherever they appear in this report or the documents incorporated by reference herein, we do not assume, and specifically disclaim, any obligation to do so, whether as a result of new information, future events or otherwise, unless required by law.

PART I

ITEM 1. Business

Overview

We are a biopharmaceutical company dedicated to advancing a broad portfolio of targeted therapeutics for oncology and other areas of unmet medical need. Our proprietary platform has delivered unique insights into cancer and related diseases. Our strategy is to leverage these biomarker insights and partner resources to advance the development of our clinical pipeline. We are focused on developing our lead candidate tivozanib in North America as a treatment for renal cell carcinoma, or RCC. In addition, we have entered into partnerships to fund the further development and commercialization of our clinical stage assets, including AV-380, ficlatuzumab, AV-203, and tivozanib for oncology indications outside of North America and for non-oncologic indications worldwide. We are currently seeking a partner to develop the AV-353 platform, a preclinical asset, worldwide for the potential treatment of pulmonary arterial hypertension, or PAH.

We have identified conditions and events that raise substantial doubt about our ability to continue as a going concern. To continue as a going concern, we must secure additional capital to provide us with additional liquidity. We believe that our approximate $23.3 million in existing cash, cash equivalents and marketable securities at December 31, 2016, could allow us to fund our planned operations into the fourth quarter of 2017; however, additional funds will be needed to extend these operations into 2018 and maintain compliance with our $10.0 million financial covenant under our loan agreement with Hercules Technology II, L.P. and Hercules Technology III, L.P., affiliates of Hercules Technology Growth, which we collectively refer to as Hercules. We expect that, in order to obtain additional capital, we will need to complete public or private financings of debt or equity, receive milestone payments from our partners, or both. We may also seek to procure additional funds through future arrangements with collaborators, licensees or other third parties, and these arrangements would generally require us to relinquish or encumber rights to some of our technologies or drug candidates. Moreover, we may not be able to receive milestone payments, complete additional financing or enter into such arrangements on acceptable terms, if at all. For a further discussion of our liquidity, please refer to Part II, Item 7 of this report under the heading “Management’s Discussion and Analysis of Financial Condition and Results of Operations—Liquidity and Capital Resources—Operating Capital Requirements and Going Concern” and Note 1 to our consolidated financial statements included elsewhere in this Annual Report on Form 10-K.

Tivozanib

Our pipeline includes our lead candidate tivozanib, an oral, once-daily, vascular endothelial growth factor, or VEGF, tyrosine kinase inhibitor, or TKI. Tivozanib is a potent, selective and long half-life inhibitor of all three VEGF receptors and is designed to optimize VEGF blockade while minimizing off-target toxicities, potentially resulting in improved efficacy and minimal dose modifications. Tivozanib has been investigated in several tumor types, including renal cell, colorectal and breast cancers.

Clinical and Regulatory Development in RCC

RCC First Line Phase 3 Trial (TIVO-1): We conducted a global phase 3 clinical trial, which we refer to as the TIVO-1 trial, comparing the efficacy and safety of tivozanib with Nexavar® (sorafenib), an approved therapy, for first-line treatment of RCC. The trial met its primary endpoint for progression-free survival, or PFS, but showed a non-statistically significant trend favoring the sorafenib arm in overall survival, or OS. In June 2013, the U.S. Food and Drug Administration, or FDA, issued a complete response letter informing us that it would not approve tivozanib for the first-line treatment of advanced RCC based solely on the data from this trial, and recommended that we perform an additional clinical trial adequately sized to assure the FDA that there is no adverse effect on OS.

TIVO-1 Extension Study - One-way crossover from sorafenib to tivozanib (Study 902): We completed a TIVO-1 extension study in which patients with advanced RCC received tivozanib as second-line treatment subsequent to

disease progression on the sorafenib arm in the TIVO-1 first-line RCC trial. We presented the final results at the 2015 American Society of Clinical Oncology (ASCO) Annual Meeting on June 1, 2015. The final results showed a median PFS of 11.0 months and a median OS of 21.6 months, demonstrating the clinically meaningful efficacy of tivozanib in a VEGF treatment refractory population. We believe that the long OS derived from tivozanib following sorafenib that was demonstrated in Study 902 contributed to the discordance in the efficacy results in the TIVO-1 trial between the PFS benefit, which significantly favored tivozanib, and the OS, which trended in favor of sorafenib. However, the FDA did not accept this explanation, finding that the OS results were uninterpretable, and recommended that we perform a second phase 3 trial, as set forth above.

European Marketing Authorization Application by EUSA. Tivozanib has previously been granted orphan drug designation in Europe for the treatment of RCC. Our licensee, EUSA Pharma (UK) Limited, or EUSA, submitted a marketing authorization application, or MAA, for tivozanib for the treatment of RCC to the European Medicines Agency, or EMA, in February 2016 based primarily on our existing dataset, which includes the results from the TIVO-1 clinical trial of tivozanib in the first-line treatment of

RCC, combined with the TIVO-1 extension trial, and one phase 1 and two phase 2 trials in RCC. The EMA validated the MAA in March 2016, confirming that the submission was complete and that it would initiate its review process. EUSA received the Day 120 List of Questions from the Committee for Medicinal Products for Human Use, or CHMP, of the EMA in July 2016, and submitted its responses in November 2016. In January 2017, EUSA received the Day 180 List of Outstanding Issues, or LOI, from the CHMP. The Day 180 LOI signifies that the MAA is not approvable at the present time, and outlines outstanding deficiencies, which are then required to be satisfactorily addressed in an oral explanation and/or in writing prior to a final application decision. EUSA has informed us that it expects to submit written responses to the Day 180 LOI in April 2017, and the EMA has tentatively scheduled EUSA to provide an oral explanation to the CHMP in May 2017.

RCC Third Line Phase 3 Trial (TIVO-3): In May 2016, we initiated enrollment and treatment of patients in a phase 3 trial of tivozanib in the third-line treatment of patients with refractory RCC, which we refer to as the TIVO-3 trial. The TIVO-3 clinical trial was designed to address the OS concerns from the TIVO-1 trial presented in the June 2013 complete response letter from the FDA and to support a request for regulatory approval of tivozanib in the United States as a third-line treatment and as a first-line treatment for RCC. Our trial design, which we reviewed with the FDA, provides for a randomized, controlled, multi-center, open-label phase 3 clinical trial of approximately 322 subjects randomized 1:1 to receive either tivozanib or sorafenib. Subjects enrolled in the trial must have failed two systemic therapies one of which must have been a VEGF TKI. Patients may have received prior immunotherapy, including immune checkpoint (PD-1) inhibitors, reflecting a potentially evolving treatment landscape. The primary objective of the TIVO-3 trial is to show improved PFS, and secondary endpoints include OS, safety and objective response rate, or ORR. The trial's sites are located in North America and Europe. The TIVO-3 trial does not include a crossover design, meaning that patients who progress in one therapy will not then be offered the opportunity to cross over to the other therapy. We expect to complete enrollment in the TIVO-3 trial in June 2017, and to report top line data in the first quarter of 2018. The TIVO-3 trial passed an initial safety data assessment in February 2017. We expect a pre-planned interim futility analysis to occur mid-year 2017.

RCC PD-1 Combination Trial with Opdivo (TiNivo): In March 2017, we initiated enrollment in a phase 1/2 clinical trial of tivozanib in combination with Opdivo® (nivolumab), an immune checkpoint (PD-1) inhibitor, for the treatment of RCC, which we refer to as the TiNivo trial. Bristol-Myers Squibb is supplying nivolumab for the TiNivo trial, and we are the trial sponsor. In recent clinical trials, TKIs and PD-1 inhibitors have shown promising efficacy in treating RCC in combination. However, several TKI/PD-1 combinations have encountered toxicity levels that we believe are likely to challenge or prohibit such TKIs from safely combining with PD-1 inhibitors for RCC treatment. In our clinical trials, tivozanib has demonstrated a superior tolerability profile relative to certain other TKIs, including lower rates of key potential overlapping toxicities with PD-1 inhibitors. We believe that tivozanib's tolerability profile has the potential to allow tivozanib to combine with PD-1 inhibitors more safely than other TKIs. The TiNivo trial is being led by the Institut Gustave Roussy in Paris under the direction of Professor Bernard Escudier, MD, Chairman of the Genitourinary Oncology Committee. The phase 1 trial will primarily evaluate the safety of tivozanib in combination with nivolumab at escalating doses of tivozanib and, assuming favorable results, is expected to be followed by a phase 2 expansion at the established combination dose. We expect to receive initial data from the phase 1 portion of the TiNivo trial in the first half of 2017.

Tivozanib Partnerships

In-License from KHK. In 2006, we acquired the exclusive rights to develop and commercialize tivozanib in all countries outside of Asia and the Middle East under a license from Kyowa Hakko Kirin Co., Ltd. (formerly Kirin Brewery Co. Ltd.), or KHK.

EUSA License Agreement: In December 2015, we entered into a license agreement with EUSA, under which we granted EUSA the right to develop and commercialize tivozanib for all diseases and conditions in humans, excluding non-oncologic diseases or conditions of the eye, in Europe (excluding Russia, Ukraine and the Commonwealth of Independent States), Latin America (excluding Mexico), Africa, Australasia and New Zealand.

Ficlatuzumab

Ficlatuzumab is a potent 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. In April 2014, we and Biodesix, Inc., or Biodesix, entered into a worldwide Co-Development and Collaboration Agreement, or the Biodesix Agreement, to develop and commercialize ficlatuzumab.

We have completed two phase 1 clinical studies of ficlatuzumab administered as a single agent and in combination with erlotinib, an endothelial growth factor receptor, or EGFR, TKI. We also performed a phase 2 clinical trial evaluating ficlatuzumab in combination with gefitinib, an EGFR TKI, 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, or ITT, population. However, a retrospective exploratory subgroup analysis utilizing Biodesix's companion diagnostic, VeriStrat®, identified a sub-population of patients who experienced a progression free survival and overall survival benefit from the addition of ficlatuzumab to gefitinib. In December 2014, we and Biodesix initiated the

FOCAL trial, a phase 2 confirmatory study of ficlatuzumab in combination with erlotinib in the subset of patients with first-line advanced NSCLC previously identified. After experiencing lower rates of positivity for the two markers and slower than expected enrollment, a blinded look at the FOCAL trial data from enrolled patients found that the patients, who were known to be selected for poor prognosis, experienced materially higher discontinuation rates than observed in both the general ITT population and the retrospective exploratory subgroup population of the prior phase 2 clinical trial. This observation significantly compromised the commercial opportunity and the feasibility of the FOCAL trial. Based on the findings from the interim analysis and the slow enrollment, we and Biodesix agreed in September 2016 to discontinue the FOCAL trial.

We and Biodesix are also funding an investigator-sponsored clinical trial of ficlatuzumab in combination with ERBITUX® (cetuximab) in squamous cell carcinoma of the head and neck. We anticipate that we will present preliminary clinical observations from this phase 1 trial at an upcoming scientific conference. We and Biodesix are also funding an investigator-sponsored clinical trial of ficlatuzumab in combination with Cytosar (cytarabine) in acute myeloid leukemia. We anticipate that we will present preliminary clinical observations from this phase 1 trial at an upcoming scientific conference. We continue to evaluate several additional opportunities for the further clinical development of ficlatuzumab.

AV-203

AV-203 is a potent anti-ErbB3 (also known as HER3) specific monoclonal antibody with high ErbB3 affinity. We have observed potent anti-tumor activity in mouse models. AV-203 selectively inhibits the activity of the ErbB3 receptor, and our preclinical studies suggest that neuregulin-1, or NRG1 (also known as heregulin), levels predict AV-203 anti-tumor activity. We have completed a phase 1 dose escalation study of AV-203, which established a recommended phase 2 dose, demonstrated good tolerability and promising early signs of activity, and reached the maximum planned dose of AV-203 monotherapy. In 2014, the expansion cohort of this trial was discontinued to conserve capital resources.

In March 2016, we entered into a collaboration and license agreement with CANbridge Life Sciences Ltd., or CANbridge, under which we granted CANbridge the exclusive right to develop, manufacture and commercialize AV-203 in all countries other than the United States, Canada and Mexico. CANbridge has begun its work to optimize the manufacturing of AV-203. CANbridge expects that AV-203 will reenter the clinic in 2018.

AV-380

AV-380 is a potent humanized IgG1 inhibitory monoclonal antibody targeting growth differentiating factor-15, or GDF15, a divergent member of the TGF-ß family, for the potential treatment or prevention of cachexia. Cachexia 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. Cachexia is associated with various cancers as well as chronic kidney disease, congestive heart failure, chronic obstructive pulmonary disease, or COPD, and other diseases. We believe that AV-380 represents a unique approach to treating cachexia because it addresses key underlying mechanisms of the syndrome. AV-380 focuses on a significant area of patient need. It is estimated that approximately 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 alone, the estimated prevalence of cancer cachexia is over 400,000 patients, and the prevalence of cachexia due to cancer, COPD, congestive heart failure, frailty and end stage renal disease combined is estimated to total more than 5 million patients (Am J Clin Nutr 2006).

We have demonstrated preclinical proof-of-concept for AV-380 in multiple cancer cachexia models and have completed cell line development. In September 2014, we presented the results from four preclinical studies of AV-380 in various in vivo cachexia models and in vitro assays at the 2nd Cancer Cachexia Conference in Montreal, Canada. Our research was also selected for presentation in an oral session at the conference. In April 2015, we also

presented the results from a preclinical study of AV-380 in a cachectic human tumor xenograft model at the Annual Meeting of the American Association of Cancer Research. We have established preclinical proof-of-concept for GDF15 as a key driver of cachexia by demonstrating, in animal models, that the administration of GDF15 induces cachexia, and that inhibition of GDF15 reverses cachexia and provides a potential indication of an overall survival benefit.

In August 2015, we entered into a license agreement under which we granted Novartis International Pharmaceutical Ltd., or Novartis, the exclusive right to develop and commercialize AV-380 and our related antibodies. Under this agreement, Novartis is responsible for all activities and costs associated with the further development, regulatory filing and commercialization of AV-380 worldwide. In connection with the AV-380 program, we have in-licensed certain patents and patent applications from St. Vincent's Hospital Sydney Limited in Sydney, Australia, which we refer to as St. Vincent's.

AV-353 Platform

The AV-353 platform includes a number of potent inhibitory antibody candidates specific to Notch 3. The Notch 3 pathway is important in cell-to-cell communication involving gene regulation mechanisms that control multiple cell differentiation processes during the entire life cycle. Scientific literature has implicated the Notch 3 receptor pathway in multiple diseases, including cancer, cardiovascular diseases and neurodegenerative conditions. Publications, including Nature Medicine (2009), have implicated the Notch 3 pathway in PAH, a rare and life-threatening disorder that affects approximately 250,000 people worldwide (Global Data 2016 PAH Opportunity Analyzer; 2012 Decision Resources PAH Report) and is caused by enlargement of the arterial walls in small arteries between the heart and the lungs, resulting in restricted blood flow. Currently, no known cure for PAH exists. Existing treatments for PAH have focused on controlling symptoms by avoiding vasoconstriction and increasing vasodilation of blood vessels but have not reversed the underlying cause of the disease. However, the results of a recently concluded pre-clinical research study conducted at the University of California at San Diego (and recently presented in a poster at the November 2016 American Heart Association meeting) using one of our anti-Notch3 antibody candidates, generated preclinical data that supports the ability of the antibody to potentially reverse the thickening of vascular smooth muscle cells, which would represent a disease-modifying approach to treatment. A manuscript of the results is being prepared for submission to a peer-reviewed journal.

We are seeking patent protection of our AV-353 platform, which was developed utilizing our research and development platform and have already filed composition of matter patent applications. We are currently seeking a partner to develop the AV-353 platform worldwide for the potential treatment of PAH.

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, but not limited to, Roche Laboratories, Inc., or Roche, Pfizer Inc., or Pfizer, Bayer HealthCare AG, or Bayer, Amgen, Inc., Eli Lilly and Company, or Lilly, GlaxoSmithKline plc, or GSK, Xbiotech Inc., Novartis, Bristol-Myers Squibb Company, Merck & Co., Merrimack Pharmaceuticals, Inc., Arqule, Inc., Exelixis, Inc., Eisai Co., Ltd., Merck KGaA and AstraZeneca plc are pursuing the development or are currently marketing pharmaceuticals that target VEGF, HGF, ErbB3, Notch 3 or other pathways that could compete with our development candidates in oncology, cachexia, age-related macular degeneration, or AMD, and PAH. 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, cachexia, AMD, and PAH 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.

Tivozanib

There are currently eleven FDA-approved drugs in oncology which target the VEGF receptors. Eight 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 Pharmaceuticals Inc., a subsidiary of Amgen, Sutent (sunitinib) and Inlyta (axitinib) are marketed by Pfizer, and Votrient (pazopanib) is marketed by

Novartis. Most of these approved VEGF TKIs are not specific to the VEGF 1, 2 and 3 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, Kisplyx (lenvatinib) marketed by Eisai in combination with everolimus and Cometriq/Cabometyx (cabozantinib), marketed by Exelixis, are approved for RCC.

Avastin (bevacizumab), marketed by Roche/Genentech, Inc., is a monoclonal antibody approved for intravenous administration 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 S.A. and Regeneron Pharmaceuticals, Inc., 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 metastatic

CRC. Cyramza (ramucirumab), marketed by Lilly, is an antibody that binds to the VEGF-2 receptor that is approved for the treatment of advanced gastric or gastro-esophageal junction adenocarcinoma and in combination with docetaxel for the treatment of NSCLC.

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

In addition, the emergence of PD-1/PD-L1 inhibitor therapies present additional competition for tivozanib in advanced RCC. For example, Opdivo (nivolumab), marketed by Bristol-Myers Squibb, is an approved anti-PD-1 for second line RCC. Additional clinical trials that are testing mono and combination therapies of PD-1/PD-L1 with other immuno-oncology targets and VEGF TKIs targeting RCC are in the pipeline. We are aware of several ongoing phase 3 registration studies evaluating PD-1/PD-L1 inhibitors in combination with VEGF TKIs in RCC as well as combinations of PD-1 agents in combination with other immune therapies for RCC.

Ficlatuzumab

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 Amgen's AMG-102 (rilotumumab), initiated in a phase 3 clinical trial (which has been discontinued), as well as Lilly's c-Met receptor antibody LY-2875358, currently in multiple phase 2 trials. In addition, Roche has conducted multiple phase 3 trials for a c-Met receptor antibody onartuzumab (MetMAb/ 5D5 Fab). Roche 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. ArQule, Inc. and Daiichi Sankyo, Inc., under a collaboration agreement, completed a phase 3 trial of ARQ-197 (tivantinib) in liver cancer that failed to meet its primary endpoint.

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), 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 U.S. LLC's SAR-125844, EMD Serono, Inc.'s MSC2156119J, Amgen BioPharma's AMG-337 and AMG-208, Lilly's merestinib (LY2801653), Les Laboratoires Servier SAS's S-49076, AstraZeneca and Hutchison MediPharma Limited's savolitinib, Merck KGaA's tepotinib, AbbVie Inc.'s ABT-700, Deciphera Pharmaceuticals, LLC's altiratinib, Betta Pharmaceuticals Co., Ltd.'s BPI-9016 and Bristol-Myers Squibb Company's and Aslan Pharmaceuticals' BMS-777607.

AV-203

We believe the most direct competitors to our AV-203 program are monoclonal antibodies that specifically target the ErbB3 receptor, including Merrimack Pharmaceuticals, Inc.'s MM-121, which is currently in pivotal phase 2 clinical development, and Daiichi Sankyo, Inc.'s and Amgen, Inc.'s patritumab (AMG-888), which recently entered phase 2 clinical development for head and neck cancer and metastatic breast cancer. Other clinical-stage ErbB3-specific competitors include Roche's RG-7116, Novartis's elgemtumab, Regeneron's REGN1400, GSK's GSK-2849330, Merus N.V.'s MCLA-128, AstraZeneca's sapitinib, Celldex Therapeutics Inc.'s KTN-3379 and Sihuan Pharmaceutical Holdings Group Ltd.'s pirotinib and sirotinib. Clinical stage competitors targeting ErbB3 in addition to other targets include Roche's MEHD7945A, and Merrimack Pharmaceuticals MM-111 and MM-141.

AV-380 Program in Cachexia

Only a limited number of agents have been approved for the treatment or prevention of cachexia caused by any disease. In the United States, Megace is the only approved agent for the treatment of cachexia (in patients with the diagnosis of AIDS). Megace and medroxyprogesterone are approved for cancer cachexia in Europe. Three agents have

recently completed or are currently being studied 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. The trials suggested limited benefits in a larger patient population and the company has discontinued its commercialization efforts. Another agent that has recently completed phase 3 trials is Helsinn's anamorelin, for which Helsinn filed for EMA approval in 2015 for treating 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 and has shown encouraging overall survival results.

A number of agents with different mechanisms of action have completed or 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 Biotherapeutics, Inc.'s PINTA 745. Of these, both Lilly's LY2495655 and PINTA 745 have announced failures to demonstrate clinical proof of concept in their respective phase 2 trials. 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 Alder Biotherapeutics Inc.'s clazakizumab (ALD-518, targeting IL-6), PsiOxus Therapeutics, Ltd.'s MT-102 (dual acting catabolic/anabolic transforming agent), Acacia Pharma Group plc's APD-209 (progestin/ß2 antagonist) and Ohr Pharmaceutical, Inc.'s OHR118 (cytoprotectant/immunomodulator). PsiOxus's espindolol has completed phase 1 trials.

AV-353 Platform

There are currently no Notch 3-specific inhibitors approved or in clinical trials in oncology or PAH indications. Pfizer recently stopped development of PF-06650808, a Notch 3-specific antibody drug conjugate which was in phase 1 trials in multiple oncology indications. However, a number of agents for applications in oncology are being explored which target the Notch 3 receptor and may inhibit other Notch receptors including Notch 1, Notch 2 and Notch 4, including BMS-906024, BMS-986115, BMS-871 and Tarextumab (OMP-59R5).

There are multiple treatments approved for PAH through various other mechanisms apart from Notch 3 inhibition. These include treatments such as epithelial receptor antagonists, phosphodiesterase type 5 inhibitors, and prostacyclin analogues. We do not believe that any of these approved therapies has demonstrated disease modifying effects.

Strategic Partnerships

CANbridge

On March 16, 2016, which we refer to as the Effective Date, we entered into a collaboration and license agreement with CANbridge, or the CANbridge Agreement, under which we granted CANbridge the exclusive right to develop, manufacture and commercialize AV-203, our proprietary ErbB3 (HER3) inhibitory antibody, for the diagnosis, treatment and prevention of disease in humans and animals in all countries other than the United States, Canada and Mexico. Under the terms of the CANbridge Agreement, if we determine to grant a license to any ErbB3 inhibitory antibody in the United States, Canada or Mexico, we are obligated to first negotiate with CANbridge for the grant to CANbridge of a license to such rights. The parties have both agreed not to directly or indirectly develop or commercialize any other ErbB3 inhibitory antibody product during the term of the CANbridge Agreement other than pursuant to the CANbridge Agreement.

CANbridge has responsibility for all activities and costs associated with the further development, manufacture, regulatory filings and commercialization of AV-203 throughout its licensed territory. CANbridge is obligated to use commercially reasonable efforts to develop and obtain regulatory approval for AV-203 in each of China, Japan, the United Kingdom, France, Italy, Spain, and Germany. CANbridge will bear all costs for development of AV-203 through proof-of-concept in Esophageal Squamous Cell Carcinoma, after which we would expect to contribute to certain worldwide development costs.

Pursuant to the CANbridge Agreement, CANbridge paid us an upfront fee of $1.0 million in April 2016. CANbridge also agreed to reimburse us $1.0 million for certain manufacturing costs and expenses that we previously incurred, $0.5 million of which will be due on the earlier of (i) the date of validation by CANbridge of certain manufacturing development activities we conducted and (ii) twelve months from the Effective Date, and the remaining $0.5 million of which will be due on the earlier of (i) the date of validation by CANbridge of such manufacturing development activities or (ii) eighteen months from the Effective Date. We are also eligible to receive up to $42.0 million in potential development and regulatory milestone payments and up to $90.0 million in potential sales based milestone payments based on annual net sales of licensed products. Upon commercialization, we are eligible to receive a tiered royalty, with a percentage range in the low double-digits, on net sales of approved licensed products. CANbridge's obligation to pay royalties for each licensed product expires on a country-by-country basis on the later of the expiration of patent rights covering such licensed product in such country, the expiration of regulatory data exclusivity in such country and ten years after the first commercial sale of such licensed product in such country. A percentage of any milestone and royalty payments received by us, excluding upfront and reimbursement payments, are due to

Biogen Idec International GmbH, or Biogen Idec, as a sublicensing fee under our option and license agreement with Biogen dated March 18, 2009, as amended.

The term of the CANbridge Agreement commenced on the Effective Date and will continue until the last to expire royalty term applicable to licensed products. Either party may terminate the CANbridge Agreement in the event of a material breach of the CANbridge Agreement by the other party that remains uncured for a period of 45 days, in the case of a material breach of a payment obligation, and 90 days in the case of any other material breach. CANbridge may terminate the CANbridge Agreement without cause at any time upon 180 days' prior written notice to us. We may terminate the CANbridge Agreement upon thirty days' prior written notice if CANbridge challenges any of the patent rights licensed to CANbridge under the CANbridge Agreement.

EUSA

In December 2015, we entered into a license agreement with EUSA under which we granted to EUSA the exclusive, sublicensable right to develop, manufacture and commercialize tivozanib in the territories of Europe (excluding Russia, Ukraine and

the Commonwealth of Independent States), Latin America (excluding Mexico), Africa, Australasia and New Zealand for all diseases and conditions in humans, excluding non-oncologic diseases or conditions of the eye.

EUSA is obligated to use commercially reasonable efforts to seek regulatory approval for and commercialize tivozanib throughout its licensed territories for RCC. With the exception of certain support to be provided by us in connection with the application for marketing approval by the EMA, EUSA has responsibility for all activities and costs associated with the further development, manufacture, regulatory filings and commercialization of tivozanib in its licensed territories.

Under the license agreement, EUSA made a research and development funding payment to us of $2.5 million in 2015. EUSA is required to make a further research and development funding payment of $4.0 million if the EMA grants marketing approval for tivozanib for treatment of RCC. We are eligible to receive additional research funding from EUSA, including up to $20.0 million for the data generated from our phase 3 clinical trial in third-line RCC if EUSA elects to utilize such data for regulatory or commercial purposes, and up to $2.0 million for the data generated from a phase 1 combination trial with a checkpoint inhibitor if EUSA elects to utilize such data for regulatory or commercial purposes. We would be entitled to receive milestone payments of $2.0 million per country upon reimbursement approval, if any, for RCC in each of France, Germany, Italy, Spain and the United Kingdom, and an additional $2.0 million for the grant of marketing approval, if any, in three of the following five countries: Argentina, Australia, Brazil, South Africa and Venezuela. We are also eligible to receive a payment of $2.0 million in connection with a filing by EUSA with the EMA for marketing approval, if any, for tivozanib for the treatment of each of up to three additional indications and $5.0 million per indication in connection with the EMA's grant of marketing approval for each of up to three additional indications, as well as up to $335.0 million upon EUSA's achievement of certain sales thresholds. We are also eligible to receive tiered double digit royalties on net sales, if any, of licensed products in its licensed territories ranging from a low double digit up to mid-twenty percent depending on the level of annual net sales. Thirty percent of any non-research and development related milestones and royalty payments we receive is due to KHK as a sublicensing fee under our license agreement with KHK. The research and development funding payments under the EUSA license agreement are not subject to sublicensing payment to KHK.

The term of the license agreement commenced on the effective date and will continue on a product-by-product and country-by-country basis until the later to occur of (a) the expiration of the last valid patent claim for such product in such country, (b) the expiration of market or regulatory data exclusivity for such product in such country or (c) the 10th anniversary of the effective date. Either party may terminate the license agreement in the event of the bankruptcy of the other party or a material breach by the other party that remains uncured, following receipt of written notice of such breach, for a period of (a) thirty (30) days in the case of breach for nonpayment of any amount due under the license agreement, and (b) ninety (90) days in the case of any other material breach. EUSA may terminate the license agreement at any time upon one hundred eighty (180) days' prior written notice. In addition, we may terminate the license agreement upon thirty (30) days' prior written notice if EUSA challenges any of the patent rights licensed under the license agreement.

Novartis

In August 2015, we entered into a license agreement with Novartis, under which we granted Novartis the exclusive right to develop and commercialize AV-380 and our related antibodies that bind to GDF15 worldwide. Under this agreement, Novartis is responsible for all activities and costs associated with the further development, regulatory filing and commercialization of AV-380 worldwide.

Novartis made an upfront payment to us of $15.0 million in September 2015. We are also eligible to receive (a) up to $53.0 million in potential clinical milestone payments and up to $105.0 million in potential regulatory milestone payments tied to the commencement of clinical trials and to regulatory approvals of products developed under the license agreement in the United States, the European Union and Japan; and (b) up to $150.0 million in potential sales based milestone payments based on annual net sales of such products. Upon commercialization, we are eligible to

receive tiered royalties on net sales of approved products ranging from the high single digits to the low double-digits. Novartis has responsibility under the license agreement for the development, manufacture and commercialization of the licensed antibodies and any resulting approved therapeutic products. In December 2015, Novartis also exercised its right under the license agreement to acquire our inventory of clinical quality drug substance, reimbursing us approximately $3.5 million for such existing inventory.

Certain milestones achieved by Novartis would trigger milestone payment obligations from us to St. Vincent's, under our amended and restated license agreement with St. Vincent's. In addition, royalties on approved products, if any, will be payable to St. Vincent's, and we and Novartis will share that obligation equally.

The term of the license agreement commenced in August 2015 and will continue on a country-by-country basis until the later to occur of the 10th anniversary of the first commercial sale of a product in such country or the expiration of the last valid patent claim for a product in that country. We or Novartis may terminate the license agreement in the event of a material breach by the other party that remains uncured for a period of sixty (60) days, which period may be extended an additional thirty (30) days under certain

circumstances. Novartis may terminate the license agreement, either in its entirety or with respect to any individual products or countries, at any time upon sixty (60) days' prior written notice. In addition, we may terminate the license agreement upon thirty (30) days' prior written notice if Novartis challenges certain patents controlled by us related to our antibodies.

Biodesix

In April 2014, we and Biodesix entered into the Biodesix Agreement to develop and commercialize ficlatuzumab. Under the Biodesix Agreement, we granted Biodesix perpetual, non-exclusive rights to certain intellectual property, including all clinical and biomarker data related to ficlatuzumab, to develop and commercialize VeriStrat®, Biodesix's proprietary companion diagnostic test. Biodesix granted us perpetual, non-exclusive rights to certain intellectual property, including diagnostic data related to VeriStrat, with respect to the development and commercialization of ficlatuzumab; each license includes the right to sublicense, subject to certain exceptions. Pursuant to a joint development plan, we retain primary responsibility for clinical development of ficlatuzumab. In September 2016, we and Biodesix announced the termination of the FOCAL trial, a phase 2 proof-of-concept clinical study of ficlatuzumab in which VeriStrat was used to select clinical trial subjects.

Under the Biodesix Agreement, with the exception of the costs incurred for the FOCAL trial, we and Biodesix are each required to contribute 50% of all clinical, regulatory, manufacturing and other costs to develop ficlatuzumab. Pursuant to the Biodesix Agreement, Biodesix was obligated to fund all costs of the FOCAL trial up to a cap of $15 million, following which all costs of the FOCAL trial would be shared equally. In connection with the discontinuation of the FOCAL trial, on October 14, 2016, we and Biodesix amended the Biodesix Agreement. Under the amendment, we agreed to share 50% of all the program costs from August 1, 2016 forward. In return for bearing 50% of the FOCAL costs after August 1, 2016, we will be entitled to recover an agreed multiple of the additional costs borne by us out of any income Biodesix receives from the partnership in connection with the licensing, development or commercialization of ficlatuzumab. We do not anticipate that these remaining costs will be material. Following such recovery, the payment structure under the original Biodesix Agreement, which generally provides that the parties share equally in any costs and revenue, will resume without such modification.

Pending marketing approval or the sublicense of ficlatuzumab, and subject to the negotiation of a commercialization agreement, each party would share equally in commercialization profits and losses, subject to our right to be the lead commercialization party.

Prior to the first commercial sale of ficlatuzumab, each party has the right to elect to discontinue participating in further development or commercialization efforts with respect to ficlatuzumab, which is referred to as an "Opt-Out". If either we or Biodesix elects to Opt-Out, with such party referred to as the "Opting-Out Party," then the Opting-Out Party shall not be responsible for any future costs associated with developing and commercializing ficlatuzumab other than any ongoing clinical trials. If we elect to Opt-Out, we will continue to make the existing supply of ficlatuzumab available to Biodesix for the purposes of enabling Biodesix to complete the development of ficlatuzumab, and Biodesix will have the right to commercialize ficlatuzumab. After election of an Opt-Out, the non-opting out party shall have sole decision-making authority with respect to further development and commercialization of ficlatuzumab. Additionally, the Opting-Out Party shall be entitled to receive, if ficlatuzumab is successfully developed and commercialized, a royalty equal to 10% of net sales of ficlatuzumab throughout the world, if any, subject to offsets under certain circumstances.

Prior to any Opt-Out, the parties shall share equally in any payments received from a third party licensee; provided, however, after any Opt-Out, the Opting-Out Party shall be entitled to receive only a reduced portion of such third-party payments.

The agreement will remain in effect until the expiration of all payment obligations between the parties related to development and commercialization of ficlatuzumab, unless earlier terminated.

St. Vincent's Hospital

In July 2012, we entered into a license agreement with St. Vincent's, under which we obtained an exclusive, worldwide license 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 GDF15. We believe GDF15 is a novel target for cachexia, and we are exploiting this license in our AV-380 program for cachexia. Under the agreement, we have the right to grant sublicenses subject to certain restrictions. 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.

In connection with entering into the original license agreement with St. Vincent's in July 2012, 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.

In August 2015, in connection with the execution of our license agreement with Novartis, we entered into an amended and restated agreement with St. Vincent's, pursuant to which we made an upfront payment to St. Vincent's of $1.5 million.

Under our license agreement with St. Vincent's:

- we (or any sublicensee) 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 (or a sublicensee) 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 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 GDF15 or the GDF15 receptor and that is a GDF15 antagonist, and will not license or induce any other person to do the same.
- we (or any sublicensee) are required to make milestone payments, up to an aggregate total of $18.9 million, upon the earlier of achievement of specified development and regulatory milestones or a specified date for the first indication, and upon the achievement of specified development and regulatory milestones for the second and third 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;
- we (or any sublicensee) will be required to pay tiered royalty payments equal to a low-single-digit percentage of any net sales we or our sublicensees make from licensed therapeutic products, an obligation we share with Novartis equally. 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; and
- we (or any sublicensee) will be required to 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.

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 six months' notice if we terminate our GDF15 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 GDF15 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 GDF15 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.

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.

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. In March 2014, we amended our agreement with Biogen Idec, and regained worldwide rights to AV-203. Pursuant to the amendment, we were obligated to in good faith use reasonable efforts to seek a collaboration partner to fund further development and commercialization of ErbB3-targeted antibodies. We satisfied this obligation in March 2016 upon entering into our license agreement with CANbridge. We are obligated to pay Biogen Idec a percentage of milestone payments we receive under the CANbridge agreement and single-digit royalty payments on net sales related to the sale of AV-203, up to cumulative maximum amount of $50.0 million.

Kyowa Hakko Kirin

In December 2006, we entered into a license agreement with 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 and the Middle East, where KHK has retained the rights to tivozanib. 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 KHK 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.

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 a VEGF receptor.

We have upfront, milestone and royalty payment obligations to KHK under our license agreement. Upon entering into the license agreement with KHK, we made an upfront payment in the amount of $5.0 million. In March 2010, we made a milestone payment to KHK in the amount of $10.0 million in connection with the dosing of the first patient in our first phase 3 clinical trial of tivozanib (TIVO-1). In December 2012, we made a $12.0 million milestone payment to KHK in connection with the acceptance by the FDA of our 2012 new drug application, or NDA, filing for tivozanib. Each milestone under the KHK agreement is a one-time only payment obligation. Accordingly, we did not owe KHK another milestone payment in connection with the dosing of the first patient in our TIVO-3 trial, and would not owe a milestone payment to KHK if we file an NDA with the FDA following the completion of our TIVO-3 clinical trial. If we obtain approval for tivozanib in the U.S., we would owe KHK a one-time milestone payment of $18.0 million, provided that we do not sublicense U.S. rights for tivozanib prior to obtaining a U.S. regulatory approval. If we were to sublicense the U.S. rights, the associated U.S. regulatory milestone would be replaced by a specified percentage of sublicensing revenue, as set forth below.

If we sublicense any of our rights to tivozanib to a third party, as we have done with EUSA pursuant to our license agreement, the sublicense defines the payment obligations of the sublicensee, which may vary from the milestone and royalty payment obligations under our KHK license relating to rights we retain. We are required to pay KHK a fixed 30% of amounts we receive from our sublicensees, including upfront license fees, milestone payments and royalties, but excluding amounts we receive in respect of research and development funding or equity investments, subject to certain limitations. In accordance with the sublicensing provisions of our KHK agreement, in 2011 we made a $22.5 million payment to KHK related to the upfront license payment received under a collaboration and license agreement we entered into with Astellas Pharmaceuticals, Inc., the termination of which became effective on August 11, 2014. If tivozanib is approved in the European Union, or EU, the $4.0 million research and development reimbursement milestone that would be owed to us by EUSA would not be subject to a sublicense revenue payment to KHK, nor would a research and development reimbursement payment upon an election by EUSA to use the data generated from our TIVO-3 or TiNivo trials for regulatory or commercial purposes, which could be up to $20.0 million for the

TIVO-3 data and up to $2.0 million TiNivo data. We would, however, owe KHK 30% of other, non-research and development payments we may receive from EUSA pursuant to our license agreement, including EU reimbursement approval milestones in up to five specified EU countries, EU marketing approvals for up to three additional indications beyond RCC, marketing approvals in up to three specified licensed territories outside of the EU, sales-based milestones and royalties, as set forth above.

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.

The license agreement will remain in effect until the expiration of all of our royalty and sublicense revenue obligations to KHK, determined on a product-by-product and country-by-country basis, unless we elect 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, KHK can terminate the agreement, resulting in a loss of our rights to tivozanib and an obligation to assign or license to KHK any intellectual property or other rights we may have in tivozanib, including our regulatory filings, regulatory approvals, patents and trademarks for tivozanib.

Intellectual Property Rights

Patent Rights

We continue to build a strong intellectual property portfolio, and, whenever possible, we seek to have multiple tiers of patent protection for our product candidates.

Tivozanib

With respect to tivozanib, we have exclusively licensed from KHK its patents that cover the molecule and its therapeutic use, a key step in manufacturing the molecule, and a crystal form of the molecule.

With respect to tivozanib, we have the following in-licensed patents:

- U.S.: 3 granted patents with expirations ranging from 2018 to 2023
- Europe: 3 granted patents with expirations ranging from 2018 to 2023
- Canada: 1 granted patent expiring in 2022
- Australia: 1 granted patent expiring in 2022

The U.S. patent covering the tivozanib molecule and its therapeutic use is expected to expire in 2022. However, in view of the length of time that tivozanib has been under regulatory review at the FDA, a patent term extension of up to five years may be available under The Drug Price Competition and Patent Term Restoration Act of 1984, or the Hatch-Waxman Act, which, if a five year extension were to be granted, would extend the term of this patent to 2027.

KHK has recently filed a patent application with the Japan Patent Office (Filing Date: September 13, 2016) related to a new invention corresponding to a formulation for tivozanib with ophthalmologic applications. Pursuant to the KHK license agreement, we have exclusive, sub-licensable rights to this new invention and the corresponding know-how outside of Asia and the Middle East.

In addition, we also own two issued U.S. patents that cover different biomarker tests for identifying human patients likely to respond to treatment with tivozanib, and one pending international patent application relating to the use of Neuropilin-1 as a serum-based biomarker for identifying patients, including patients with colorectal cancer, likely to respond to treatment with tivozanib.

With respect to tivozanib related technologies, we have:

- U.S.: 2 granted patents expiring in 2029
- International (PCT): 1 pending patent application, which if nationalized and granted, will expire in 2036

Ficlatuzumab

With respect to our anti-HGF platform, including ficlatuzumab, we have seven U.S. patents covering our anti-HGF antibodies, nucleic acids and expression vectors encoding the antibodies, host cells, methods of making the antibodies, and methods of treatment using the antibodies. With respect to our anti-HGF platform we have:

- U.S.: 7 granted patents with expirations ranging from 2027 to 2028
- Europe: 1 granted patent expiring in 2027
- Japan: 3 granted patents expiring in 2027

- Canada: 1 granted patent expiring in 2027
- Australia: 1 granted patent expiring in 2027

AV-203

With respect to our anti-ErbB3 platform, including AV-203, we have two U.S. patents covering our anti-ErbB3 antibodies, nucleic acids and expression vectors encoding the antibodies, host cells, and methods of making the antibodies; an allowed U.S. patent application directed to methods of treatment using our anti-ErbB3 antibodies; and a pending U.S. patent application directed to a method of predicting tumor response to our AV-203 antibody. With respect to our anti-ErbB3 platform we have:

- U.S.: 2 granted patents, and 2 pending patent applications, if granted, with expirations ranging from 2031 to 2032
- Europe: 1 granted patent, and 1 pending patent application, if granted, with expirations ranging from 2031 to 2032
- Japan: 1 granted patent, and 1 pending patent application, if granted, with expirations ranging from 2031 to 2032
- Canada: 2 pending patent applications, if granted, with expirations ranging from 2031 to 2032
- Australia: 2 pending patent applications, if granted, with expirations ranging from 2031 to 2032

Anti-GDF15 Antibodies

With respect to our anti-GDF15 platform, we have exclusively licensed certain patent rights from St. Vincent's, which include a granted U.S. patent directed to a method of increasing appetite and/or body weight upon administering an effective amount of an anti-GDF15 antibody (patent expiration 2029).

With respect to the licensed patent rights, we have:

- U.S.: 1 granted patent, and 1 pending patent application, if granted, with expirations ranging from 2025 to 2029
- Europe: 1 granted patent expiring in 2025
- Japan: 2 granted patents expiring in 2025
- Canada: 1 pending patent application, if granted, expiring in 2025
- Australia: 1 granted patent expiring in 2025

In addition, we also own an issued U.S. patent covering our GDF15 antibodies and a pending U.S. patent application directed to methods of treating cachexia and inhibiting loss of muscle mass associated with cachexia using our GDF15 antibodies. This patent and patent application, if granted, would be expected to expire in 2033. We also have two pending U.S. patent applications directed to methods of treating or preventing congestive heart failure or chronic kidney disease using GDF15 antibodies. These patent applications, if granted, would be expected to expire in 2035.

With respect to our GDF15 platform, we have:

- U.S.: 1 granted patent, and 3 pending patent applications, if granted, with expirations ranging from 2033 to 2035
- Europe: 3 pending patent applications with expirations, if granted, ranging from 2033 to 2035
- Japan: 3 pending patent applications with expirations, if granted, ranging from 2033 to 2035
- Canada: 2 pending patent applications with expirations, if granted, ranging from 2033 to 2035
- Australia: 2 pending patent applications with expirations, if granted, ranging from 2033 to 2035

AV-353 Platform

With respect to our AV-353 platform, we own a non-provisional U.S. patent application and two provisional U.S. patent applications covering our anti-Notch3 antibodies, nucleic acids and expression vectors encoding the antibodies, host cells, methods of making the antibodies, and methods of treatment using the antibodies. The non-provisional U.S. patent application, if granted, would be expected to expire in 2033, whereas the two provisional U.S. applications, if converted into a non-provisional patent application and granted, would be expected to expire in 2037.

With respect to our AV-353 platform, we have:

- U.S.: 3 pending patent applications with expirations, if granted, ranging from 2033 to 2037
- Europe: 1 pending patent application expiring, if granted, in 2033

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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 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. 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 a third party United States patent that contains 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 patent owners indicating that they believe we may need a license from them in order to avoid infringing their patent rights. 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. In the event that an owner of one or more of these patents were to bring an infringement action against us, we may have to argue that our product, its manufacture or use does not infringe a valid claim of the patent in question. Furthermore, 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.

Over the years, we have found 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 have used the results of freedom-to-operate studies to guide our research away from areas where we believed we were 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.

In spite of our 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.

Trademarks

We seek trademark protection in the U.S. and other jurisdictions where available and when appropriate. We have filed applications and obtained registrations for several trademarks intended for potential use in the marketing of Tivozanib, including the trademark FOTIVDA, which we have registered in the United States and 16 other jurisdictions, and for which we have filed applications in additional countries. We own U.S. and European Union registrations for a stylized FOTIVDA trademark. We own a U.S. registration for HUMAN RESPONSE PLATFORM, a trademark that we use in connection with our research and development. We own U.S. registrations for AVEO, AVEO (in stylized letters), THE HUMAN RESPONSE and AVEO ONCOLOGY THE HUMAN RESPONSE (in stylized letters), trademarks that we use in connection with our business in general. We have also registered AVEO as a trademark in over 20 other jurisdictions.

Manufacturing

We or our partners currently contract with third parties, to the extent we require, for the manufacture of our product candidates and intend to do so in the future for both clinical and potential commercial needs. 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 drug substance to support our ongoing and planned clinical trials. In addition, we currently engage a separate contract manufacturer to manufacture, package, label and distribute clinical supplies of tivozanib on an as–needed basis.

To date, our third-party manufacturers have met our manufacturing requirements. We believe that there are alternate sources of supply that can satisfy our current clinical or potential future 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 and Product Approval

Government authorities in the United States, at the federal, state and local level, and in other countries and jurisdictions, including the European Union, extensively regulate, among other things, the research, development, testing, manufacture, quality control, approval, packaging, storage, recordkeeping, labeling, advertising, promotion, distribution, marketing, post-approval monitoring and reporting, and import and export of pharmaceutical products. The processes for obtaining regulatory approvals in the United States and in foreign countries and jurisdictions, along with subsequent compliance with applicable statutes and regulations and other regulatory authorities, require the expenditure of substantial time and financial resources.

Review and Approval of Drugs and Biologics in the United States

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 Public Health Service Act, or PHSA, FDCA and related regulations, and other federal, state and local statutes and regulations. An applicant seeking approval to market and distribute a new drug or biological product in the United States must typically undertake the following:

- completion of preclinical laboratory tests, animal studies and formulation studies in compliance with the FDA's good laboratory practice, or GLP, regulations;
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submission to the FDA of an investigational new drug application, or IND, which must take effect before human clinical trials may begin;

- approval by an independent institutional review board, or IRB, representing each clinical site before each clinical trial may be initiated;
- performance of adequate and well-controlled human clinical trials in accordance with good clinical practices, or GCP, to establish the safety and efficacy of the proposed drug product for each indication;
- preparation and submission to the FDA of an NDA, for a drug candidate product and a biological licensing application, or BLA, for a biological product requesting marketing for one or more proposed indications;
- review by an FDA advisory committee, where appropriate or if applicable;

- satisfactory completion of one or more FDA inspections of the manufacturing facility or facilities at which the product, or components thereof, are produced to assess compliance with current Good Manufacturing Practices, or cGMP, requirements and to assure that the facilities, methods and controls are adequate to preserve the product's identity, strength, quality and purity;
- satisfactory completion of FDA audits of clinical trial sites to assure compliance with GCPs and the integrity of the clinical data;
- payment of user fees and securing FDA approval of the NDA or BLA; and
- compliance with any post-approval requirements, including the potential requirement to implement a Risk Evaluation and Mitigation Strategy, or REMS, and the potential requirement to conduct post-approval studies.

Preclinical Studies

Before an applicant begins testing a compound with potential therapeutic value in humans, the product candidate enters the preclinical testing stage. Preclinical studies include laboratory evaluation of the purity and stability of the manufactured substance or active pharmaceutical ingredient and the formulated product, as well as in vitro and animal studies to assess the safety and activity of the product candidate for initial testing in humans and to establish a rationale for therapeutic use. The conduct of preclinical studies is subject to federal regulations and requirements, including GLP regulations. The results of the preclinical tests, together with manufacturing information, analytical data, any available clinical data or literature and plans for clinical studies, among other things, are submitted to the FDA as part of an IND. Some long-term preclinical testing, such as animal tests of reproductive adverse events and carcinogenicity, and long term toxicity studies, may continue after the IND is submitted.

The IND and IRB Processes

An IND is an exemption from the FDCA that allows an unapproved product candidate to be shipped in interstate commerce for use in an investigational clinical trial and a request for FDA authorization to administer an investigational drug to humans. Such authorization must be secured prior to interstate shipment and administration of any new drug or biologic that is not the subject of an approved NDA or BLA. In support of a request for an IND, applicants must submit a protocol for each clinical trial and any subsequent protocol amendments must be submitted to the FDA as part of the IND. In addition, the results of the preclinical tests, together with manufacturing information, analytical data, any available clinical data or literature and plans for clinical trials, among other things, are submitted to the FDA as part of an IND. The FDA requires a 30-day waiting period after the filing of each IND before clinical trials may begin. This waiting period is designed to allow the FDA to review the IND to determine whether human research subjects will be exposed to unreasonable health risks. At any time during this 30-day period, or thereafter, the FDA may raise concerns or questions about the conduct of the trials as outlined in the IND and impose a clinical hold or partial clinical hold. In this case, the IND sponsor and the FDA must resolve any outstanding concerns before clinical trials can begin.

In addition to the foregoing IND requirements, an IRB representing each institution participating in the clinical trial must review and approve the plan for any clinical trial before it commences at that institution, and the IRB must conduct continuing review and reapprove the trial at least annually. The IRB must review and approve, among other things, the trial protocol and informed consent information to be provided to trial subjects. An IRB must operate in compliance with FDA regulations. Information about certain clinical trials must be submitted within specific timeframes to the National Institutes of Health, or NIH, for public dissemination on its ClinicalTrials.gov website. An IRB can suspend or terminate approval of a clinical trial at its institution, or an institution it represents, if the clinical trial is not being conducted in accordance with the IRB's requirements or if the product candidate has been associated with unexpected serious harm to patients.

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 trial. 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.

Human Clinical Studies in Support of an NDA or BLA

Clinical trials involve the administration of the investigational product to human subjects under the supervision of qualified investigators in accordance with GCP requirements, which include, among other things, the requirement that all research subjects

provide their informed consent in writing before their participation in any clinical trial. Clinical trials are conducted under written trial protocols detailing, among other things, the inclusion and exclusion criteria, the objectives of the trial, the parameters to be used in monitoring safety and the effectiveness criteria to be evaluated.

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

- Phase 1. Phase 1 studies include the initial introduction of an investigational new drug or biological product into humans. 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.
- 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 trial, 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.
- 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 4. Post-approval studies may be conducted after initial marketing approval. These studies are used to gain additional experience from the treatment of patients in the intended therapeutic indication.

Progress reports detailing the results of the clinical trials must be submitted at least annually to the FDA and more frequently if serious adverse events occur. In addition, IND safety reports must be submitted to the FDA for any of the following: serious and unexpected suspected adverse reactions; findings from other studies or animal or in vitro testing that suggest a significant risk in humans exposed to the drug; and any clinically important increase in the case of a serious suspected adverse reaction over that listed in the protocol or investigator brochure. The FDA or the sponsor or the data monitoring committee may suspend or terminate a clinical trial at any time on various grounds, including a finding that the research subjects are being exposed to an unacceptable health risk. The FDA will typically inspect one or more clinical sites to assure compliance with GCP and the integrity of the clinical data submitted.

Review of an NDA or BLA by the FDA

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 proposed 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 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 NDA and BLA are thus the vehicles through which applicants formally propose that the FDA approve a new product for marketing and sale in the United States for one or more indications. Every new product candidate must be

the subject of an approved NDA or BLA before it may be commercialized in the United States. Under federal law, the submission of most NDAs and BLAs is subject to an application user fee, which for federal fiscal year 2017 is $2,038,100. The sponsor of an approved NDA or BLA is also subject to annual product and establishment user fees, which for fiscal year 2017 are $97,750 per product and $512,200 per establishment. Certain exceptions and waivers are available for some of these fees, such as an exception from the application fee for drugs with orphan designation and a waiver for certain small businesses, an exception from the establishment fee when the establishment does not engage in manufacturing the drug during a particular fiscal year, and an exception from the product fee for a drug that is the same as another drug approved under an abbreviated pathway.

Following submission of an NDA or BLA, the FDA conducts a preliminary review of the application generally within 60 calendar days of its receipt and strives to inform the sponsor by the 74th day after the FDA's receipt of the submission to determine whether the application is sufficiently complete to permit substantive review. The FDA may request additional information rather than accept the application for filing. In this event, the application must be resubmitted with the additional information. The resubmitted application is also subject to review before the FDA accepts it for filing. Once the submission is accepted for filing, the FDA begins an in-depth substantive review. The FDA has agreed to specified performance goals in the review process of NDAs and BLAs. Under that agreement, 90% of applications seeking approval of New Molecular Entities, or NMEs, are meant to be reviewed within ten months from the date on which FDA accepts the NDA for filing, and 90% of applications for NMEs that have been designated for "priority review" are meant to be reviewed within six months of the filing date. For applications seeking approval of products that are not NMEs, the ten-month and six-month review periods run from the date that FDA receives the application. The review process and the Prescription Drug User Fee Act goal date may be extended by the FDA for three additional months to consider new information or clarification provided by the applicant to address an outstanding deficiency identified by the FDA following the original submission.

Before approving an application, the FDA typically will inspect the facility or facilities where the product is or will be manufactured. These pre-approval inspections may cover all facilities associated with an NDA or BLA submission, including drug component manufacturing (e.g., active pharmaceutical ingredients), finished drug product manufacturing, and control testing laboratories. The FDA will not approve an application 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. In addition, as a condition of approval, the FDA may require an applicant to develop a REMS. REMS use risk minimization strategies beyond the professional labeling to ensure that the benefits of the product outweigh the potential risks. To determine whether a REMS is needed, the FDA will consider the size of the population likely to use the product, seriousness of the disease, expected benefit of the product, expected duration of treatment, seriousness of known or potential adverse events, and whether the product is a new molecular entity.

The FDA may refer an application for a novel product to an advisory committee or explain why such referral was not made. Typically, an advisory committee is a panel of independent experts, including clinicians and other scientific experts, that reviews, evaluates and provides 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.

The FDA's Decision on an NDA or BLA

On the basis of the FDA's evaluation of the application and accompanying information, including the results of the inspection of the manufacturing facilities, the FDA may issue an approval letter or a complete response letter. An approval letter authorizes commercial marketing of the product with specific prescribing information for specific indications. A complete response letter generally outlines the deficiencies in the submission and may require substantial additional testing or information in order for the FDA to reconsider the application. If and when those deficiencies have been addressed to the FDA's satisfaction in a resubmission of the NDA, the FDA will issue an approval letter. The FDA has committed to reviewing such resubmissions in two or six months depending on the type of information included. Even with submission of this additional information, the FDA ultimately may decide that the application does not satisfy the regulatory criteria for approval.

If the FDA approves a product, it may limit the approved indications for use for the product, require that contraindications, warnings or precautions be included in the product labeling, require that post-approval studies, including Phase 4 clinical trials, be conducted to further assess the drug's safety after approval, require testing and surveillance programs to monitor the product after commercialization, or impose other conditions, including distribution restrictions or other risk management mechanisms, including REMS, which can materially affect the

potential market and profitability of the product. The FDA may prevent or limit further marketing of a product based on the results of post-market studies or surveillance programs. After approval, many 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.

Fast Track, Breakthrough Therapy, Priority Review and Regenerative Advanced Therapy Designations

The FDA is authorized to designate certain products for expedited review if they are intended to address an unmet medical need in the treatment of a serious or life threatening disease or condition. These programs are referred to as fast track designation, breakthrough therapy designation, priority review designation and regenerative advanced therapy designation.

Specifically, the FDA may designate a product for Fast Track review if it is intended, whether alone or in combination with one or more other products, for the treatment of a serious or life threatening disease or condition, and it demonstrates the potential to

address unmet medical needs for such a disease or condition. For Fast Track products, sponsors may have greater interactions with the FDA and the FDA may initiate review of sections of a Fast Track product's application before the application is complete. This rolling review may be available if the FDA determines, after preliminary evaluation of clinical data submitted by the sponsor, that a Fast Track product may be effective. The sponsor must also provide, and the FDA must approve, a schedule for the submission of the remaining information and the sponsor must pay applicable user fees. However, the FDA's time period goal for reviewing a Fast Track application does not begin until the last section of the application is submitted. In addition, the Fast Track designation may be withdrawn by the FDA if the FDA believes that the designation is no longer supported by data emerging in the clinical trial process.

Second, a product may be designated as a Breakthrough Therapy if it is intended, either alone or in combination with one or more other products, to treat a serious or life threatening disease or condition and preliminary clinical evidence indicates that the product may demonstrate substantial improvement over existing therapies on one or more clinically significant endpoints, such as substantial treatment effects observed early in clinical development. The FDA may take certain actions with respect to Breakthrough Therapies, including holding meetings with the sponsor throughout the development process; providing timely advice to the product sponsor regarding development and approval; involving more senior staff in the review process; assigning a cross disciplinary project lead for the review team; and taking other steps to design the clinical trials in an efficient manner.

Third, the FDA may designate a product for priority review if it is a product that treats a serious condition and, if approved, would provide a significant improvement in safety or effectiveness. The FDA determines, on a case by case basis, whether the proposed product represents a significant improvement when compared with other available therapies. Significant improvement may be illustrated by evidence of increased effectiveness in the treatment of a condition, elimination or substantial reduction of a treatment limiting product reaction, documented enhancement of patient compliance that may lead to improvement in serious outcomes, and evidence of safety and effectiveness in a new subpopulation. A priority designation is intended to direct overall attention and resources to the evaluation of such applications, and to shorten the FDA's goal for taking action on a marketing application from ten months to six months.

Finally, with passage of the 21st Century Cures Act, or the Cures Act, in December 2016, Congress authorized the FDA to accelerate review and approval of products designated as regenerative advanced therapies. A product is eligible for this designation if it is a regenerative medicine therapy that is intended to treat, modify, reverse or cure a serious or life-threatening disease or condition and preliminary clinical evidence indicates that the drug has the potential to address unmet medical needs for such disease or condition. The benefits of a regenerative advanced therapy designation include early interactions with FDA to expedite development and review, benefits available to breakthrough therapies, potential eligibility for priority review and accelerated approval based on surrogate or intermediate endpoints.

Post-Approval Regulation

Drugs and biologics manufactured or distributed pursuant to FDA approvals are subject to pervasive and continuing regulation by the FDA, including, among other things, requirements relating to recordkeeping, periodic reporting, product sampling and distribution, advertising and promotion and reporting of adverse experiences with the product. After approval, most changes to the approved product, such as adding new indications or other labeling claims, are subject to prior FDA review and approval. There also are continuing, annual user fee requirements for any marketed products and the establishments at which such products are manufactured, as well as new application fees for supplemental applications with clinical data.

In addition, manufacturers and other entities involved in the manufacture and distribution of approved products are required to register their establishments with the FDA and state agencies, and are subject to periodic unannounced inspections by the FDA and these state agencies for compliance with cGMP requirements. Changes to the manufacturing process are strictly regulated and often 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 the sponsor and any third-party manufacturers that the sponsor may decide to use. Accordingly, manufacturers must continue to expend time, money, and effort in the area of production and quality control to maintain cGMP compliance.

Once an approval is granted, the FDA may withdraw the approval if compliance with regulatory requirements and standards is not maintained or if problems occur after the product reaches the market. Later discovery of previously unknown problems with a product, including adverse events of unanticipated severity or frequency, or with manufacturing processes, or failure to comply with regulatory requirements, may result in revisions to the approved labeling to add new safety information; imposition of post-market studies or clinical trials to assess new safety risks; or imposition of distribution or other restrictions under a REMS program. Other potential consequences include, among other things:

- restrictions on the marketing or manufacturing of the product, suspension of the approval, or complete withdrawal of the product from the market or product recalls;

- fines, warning letters or holds on post-approval clinical trials;
- refusal of the FDA to approve pending NDAs or supplements to approved NDAs, or suspension or revocation of product license approvals;
    - product seizure or detention, or refusal to permit the import or export of products; or
- injunctions or the imposition of civil or criminal penalties.

The FDA strictly regulates marketing, labeling, advertising and promotion of products that are placed on the market. Products may be promoted only for the approved indications and in accordance with the provisions of the approved label. The FDA and other agencies actively enforce the laws and regulations prohibiting the promotion of off-label uses, and a company that is found to have improperly promoted off-label uses may be subject to significant liability.

In addition, the distribution of prescription pharmaceutical products is subject to the Prescription Drug Marketing Act, or PDMA, and its implementing regulations, as well as the Drug Supply Chain Security Act, or DSCA, which regulate the distribution and tracing of prescription drugs and prescription drug samples at the federal level, and set minimum standards for the regulation of drug distributors by the states. The PDMA, its implementing regulations and state laws limit the distribution of prescription pharmaceutical product samples, and the DSCA imposes requirements to ensure accountability in distribution and to identify and remove counterfeit and other illegitimate products from the market.

Generic Drugs

In 1984, with passage of the Hatch-Waxman Act, Congress established an abbreviated regulatory scheme authorizing the FDA to approve generic drugs that are shown to contain the same active ingredients as, and to be bioequivalent to, drugs previously approved by the FDA pursuant to NDAs. To obtain approval of a generic drug, an applicant must submit an abbreviated new drug application, or ANDA, to the agency. An ANDA is a comprehensive submission that contains, among other things, data and information pertaining to the active pharmaceutical ingredient, bioequivalence, drug product formulation, specifications and stability of the generic drug, as well as analytical methods, manufacturing process validation data and quality control procedures. ANDAs are “abbreviated” because they generally do not include preclinical and clinical data to demonstrate safety and effectiveness. Instead, in support of such applications, a generic manufacturer may rely on the preclinical and clinical testing previously conducted for a drug product previously approved under an NDA, known as the reference-listed drug, or RLD.

Specifically, in order for an ANDA to be approved, the FDA must find that the generic version is identical to the RLD with respect to the active ingredients, the route of administration, the dosage form, the strength of the drug and the conditions of use of the drug. At the same time, the FDA must also determine that the generic drug is “bioequivalent” to the innovator drug. Under the statute, a generic drug is bioequivalent to a RLD if “the rate and extent of absorption of the drug do not show a significant difference from the rate and extent of absorption of the listed drug...” Upon approval of an ANDA, the FDA indicates whether the generic product is “therapeutically equivalent” to the RLD in its publication “Approved Drug Products with Therapeutic Equivalence Evaluations,” also referred to as the “Orange Book.” Physicians and pharmacists consider a therapeutic equivalent generic drug to be fully substitutable for the RLD. In addition, by operation of certain state laws and numerous health insurance programs, the FDA’s designation of therapeutic equivalence often results in substitution of the generic drug without the knowledge or consent of either the prescribing physician or patient.

Under the Hatch-Waxman Act, the FDA may not approve an ANDA until any applicable period of non-patent exclusivity for the RLD has expired. The FDCA provides a period of five years of non-patent data exclusivity for a new drug containing a new chemical entity. For the purposes of this provision, a new chemical entity, or NCE, is a drug that contains no active moiety that has previously been approved by the FDA in any other NDA. An active moiety is the molecule or ion responsible for the physiological or pharmacological action of the drug substance. In cases where such NCE exclusivity has been granted, an ANDA may not be filed with the FDA until the expiration of five years unless the submission is accompanied by a Paragraph IV certification, in which case the applicant may submit its application four years following the original product approval. The FDCA also provides for a period of

three years of exclusivity if the NDA includes reports of one or more new clinical investigations, other than bioavailability or bioequivalence studies, that were conducted by or for the applicant and are essential to the approval of the application.

Biosimilars

The 2010 Patient Protection and Affordable Care Act, which was signed into law on March 23, 2010, included a subtitle called the Biologics Price Competition and Innovation Act of 2009 or BPCIA. That Act established a regulatory scheme authorizing the FDA to approve biosimilars and interchangeable biosimilars. To date, four biosimilar products have been approved by FDA for use in the United States. No interchangeable biosimilars, however, have been approved. The FDA has issued several guidance documents outlining an approach to review and approval of biosimilars. Additional guidance is expected to be finalized by FDA in the near term.

Under the Act, a manufacturer may submit an application for licensure of a biologic product that is "biosimilar to" or "interchangeable with" a previously approved biological product or "reference product." In order for the FDA to approve a biosimilar product, it must find that there are no clinically meaningful differences between the reference product and proposed biosimilar product in terms of safety, purity, and potency. For the FDA to approve a biosimilar product as interchangeable with a reference product, the agency must find that the biosimilar product can be expected to produce the same clinical results as the reference product, and (for products administered multiple times) that the biologic and the reference biologic may be switched after one has been previously administered without increasing safety risks or risks of diminished efficacy relative to exclusive use of the reference biologic.

Under the BPCIA, an application for a biosimilar product may not be submitted to the FDA until four years following the date of approval of the reference product. The FDA may not approve a biosimilar product until 12 years from the date on which the reference product was approved. Even if a product is considered to be a reference product eligible for exclusivity, another company could market a competing version of that product if the FDA approves a full BLA for such product containing the sponsor's own preclinical data and data from adequate and well-controlled clinical trials to demonstrate the safety, purity and potency of their product. The BPCIA also created certain exclusivity periods for biosimilars approved as interchangeable products. At this juncture, it is unclear whether products deemed "interchangeable" by the FDA will, in fact, be readily substituted by pharmacies, which are governed by state pharmacy law.

Orphan Drug Designation and Exclusivity

Under the Orphan Drug Act, the FDA may designate a drug product as an "orphan drug" if it is intended to treat a rare disease or condition, generally meaning that it affects fewer than 200,000 individuals in the United States, or more in cases in which there is no reasonable expectation that the cost of developing and making a drug product available in the United States for treatment of the disease or condition will be recovered from sales of the product. A company must request orphan drug designation before submitting an NDA or BLA for the candidate product. If the request is granted, the FDA will disclose the identity of the therapeutic agent and its potential use. Orphan drug designation does not shorten the Prescription Drug User Fee Act, or PDUFA, goal dates for the regulatory review and approval process, although it does convey certain advantages such as tax benefits and exemption from the PDUFA application fee.

If a product with orphan designation receives the first FDA approval for the disease or condition for which it has such designation or for a select indication or use within the rare disease or condition for which it was designated, the product generally will receive orphan drug exclusivity. Orphan drug exclusivity means that the FDA may not approve another sponsor's marketing application for the same drug for the same indication for seven years, except in certain limited circumstances. Orphan exclusivity does not block the approval of a different product for the same rare disease or condition, nor does it block the approval of the same product for different indications. If a drug or biologic designated as an orphan drug ultimately receives marketing approval for an indication broader than what was designated in its orphan drug application, it may not be entitled to exclusivity. Orphan exclusivity will not bar approval of another product under certain circumstances, including if a subsequent product with the same drug or biologic for the same indication is shown to be clinically superior to the approved product on the basis of greater efficacy or safety, or providing a major contribution to patient care, or if the company with orphan drug exclusivity is not able to meet market demand.

Pediatric Exclusivity

Pediatric exclusivity is another type of non-patent marketing exclusivity in the United States and, if granted, provides for the attachment of an additional six months of marketing protection to the term of any existing regulatory exclusivity, including the non-patent and orphan exclusivity. This six-month exclusivity may be granted if an NDA or BLA sponsor submits pediatric data that fairly respond to a written request from the FDA for such data. The data do not need to show the product to be effective in the pediatric population studied; rather, if the clinical trial is deemed to

fairly respond to the FDA's request, the additional protection is granted. If reports of requested pediatric studies are submitted to and accepted by the FDA within the statutory time limits, whatever statutory or regulatory periods of exclusivity or patent protection cover the product are extended by six months. This is not a patent term extension, but it effectively extends the regulatory period during which the FDA cannot approve another application.

FDA Approval and Regulation of Companion Diagnostics

If safe and effective use of a therapeutic depends on an in vitro diagnostic, then the FDA generally will require approval or clearance of that diagnostic, known as a companion diagnostic, at the same time that the FDA approves the therapeutic product. In August 2014, the FDA issued final guidance clarifying the requirements that will apply to approval of therapeutic products and in vitro companion diagnostics. According to the guidance, if FDA determines that a companion diagnostic device is essential to the safe and effective use of a novel therapeutic product or indication, FDA generally will not approve the therapeutic product or new therapeutic product indication if the companion diagnostic device is not approved or cleared for that indication. Approval or clearance of the companion diagnostic device will ensure that the device has been adequately evaluated and has adequate performance characteristics in the intended population. The review of in vitro companion diagnostics in conjunction with the review of our

therapeutic treatments for cancer will, therefore, likely involve coordination of review by the FDA's Center for Drug Evaluation and Research and the FDA's Center for Devices and Radiological Health Office of In Vitro Diagnostics Device Evaluation and Safety.

Under the FDCA, in vitro diagnostics, including companion diagnostics, are regulated as medical devices. In the United States, the FDCA and its implementing regulations, and other federal and state statutes and regulations govern, among other things, medical device design and development, preclinical and clinical testing, premarket clearance or approval, registration and listing, manufacturing, labeling, storage, advertising and promotion, sales and distribution, export and import, and post market surveillance. Unless an exemption applies, diagnostic tests require marketing clearance or approval from the FDA prior to commercial distribution. The two primary types of FDA marketing authorization applicable to a medical device are premarket notification, also called 510(k) clearance, and premarket approval, or PMA approval.

The 21st Century Cures Act

On December 13, 2016, President Obama signed the Cures Act into law. The Cures Act is designed to modernize and personalize healthcare, spur innovation and research, and streamline the discovery and development of new therapies through increased federal funding of particular programs. It authorizes increased funding for the FDA to spend on innovation projects. The new law also amends the Public Health Service Act to reauthorize and expand funding for the National Institutes of Health. The Act establishes the NIH Innovation Fund to pay for the cost of development and implementation of a strategic plan, early stage investigators and research. It also charges NIH with leading and coordinating expanded pediatric research. Further, the Cures Act directs the Centers for Disease Control and Prevention to expand surveillance of neurological diseases.

With amendments to the FDCA and the Public Health Service Act, or PHSA, Title III of the Cures Act seeks to accelerate the discovery, development, and delivery of new medicines and medical technologies. To that end, and among other provisions, the Cures Act reauthorizes the existing priority review voucher program for certain drugs intended to treat rare pediatric diseases until 2020; creates a new priority review voucher program for drug applications determined to be material national security threat medical countermeasure applications; revises the FDCA to streamline review of combination product applications; requires FDA to evaluate the potential use of "real world evidence" to help support approval of new indications for approved drugs; provides a new "limited population" approval pathway for antibiotic and antifungal drugs intended to treat serious or life-threatening infections; and authorizes FDA to designate a drug as a "regenerative advanced therapy," thereby making it eligible for certain expedited review and approval designations.

Review and Approval of Drug Products in the European Union

In order to market any product outside of the United States, a company must also comply with numerous and varying regulatory requirements of other countries and jurisdictions regarding quality, safety and efficacy and governing, among other things, clinical trials, marketing authorization, commercial sales and distribution of drug products. Whether or not it obtains FDA approval for a product, the company would need to obtain the necessary approvals by the comparable foreign regulatory authorities before it can commence clinical trials or marketing of the product in those countries or jurisdictions. The approval process ultimately varies between countries and jurisdictions and can involve additional product testing and additional administrative review periods. The time required to obtain approval in other countries and jurisdictions might differ from and be longer than that required to obtain FDA approval. Regulatory approval in one country or jurisdiction does not ensure regulatory approval in another, but a failure or delay in obtaining regulatory approval in one country or jurisdiction may negatively impact the regulatory process in others.

Clinical Trial Approval in the EU

Pursuant to the currently applicable Clinical Trials Directive 2001/20/EC and the Directive 2005/28/EC on Good Clinical Practice, or GCP, an applicant must obtain approval from the competent national authority of the EU Member State in which the clinical trial is to be conducted. If the clinical trial is conducted in different EU Member States, the competent authorities in each of these EU Member States must provide their approval for the conduct of the clinical trial. Furthermore, the applicant may only start a clinical trial at a specific trial site after the competent ethics committee has issued a favorable opinion.

In April 2014, the EU adopted a new Clinical Trials Regulation (EU) No 536/2014, which is set to replace the current Clinical Trials Directive 2001/20/EC. The new Clinical Trials Regulation will be directly applicable to and binding in all 28 EU Member States without the need for any national implementing legislation. The new Clinical Trials Regulation (EU) No 536/2014 was designed to only become applicable no earlier than 28 May 2016. It will overhaul the current system of approvals for clinical trials in the EU. Specifically, the new legislation aims at simplifying and streamlining the approval of clinical trials in the EU. Under the new coordinated procedure for the approval of clinical trials, the sponsor of a clinical trial will be required to submit a single application for approval of a clinical trial to a reporting EU Member State (RMS) through an EU Portal. The submission procedure will be the same irrespective of whether the clinical trial is to be conducted in a single EU Member State or in more than one EU Member State. The Clinical Trials Regulation also aims to streamline and simplify the rules on safety reporting for clinical trials.

Marketing Authorization

In the EU, marketing authorizations for medicinal products may be obtained through several different procedures founded on the same basic regulatory process.

The centralized procedure provides for the grant of a single marketing authorization that is valid for all EU Member States. The centralized procedure is compulsory for medicinal products produced by certain biotechnological processes, products designated as orphan medicinal products, and products with a new active substance indicated for the treatment of certain diseases. It is optional for those products that are highly innovative or for which a centralized process is in the interest of patients. Under the centralized procedure in the EU, the maximum timeframe for the evaluation of a MAA 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 may be granted by the CHMP in exceptional cases. These are defined as circumstances in which a medicinal product is expected to be of a “major public health interest.” Three cumulative criteria must be fulfilled in such circumstances: the seriousness of the disease, such as severely 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 these circumstances, the EMA ensures that the opinion of the CHMP is given within 150 days.

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.

The decentralized procedure provides for approval by one or more other concerned EU Member States of an assessment of an application for marketing authorization conducted by one EU Member State, known as the reference EU Member State. In accordance with this procedure, an applicant submits an application for marketing authorization to the reference EU Member State and the concerned EU Member States. This application is identical to the application that would be submitted to the EMA for authorization through the centralized procedure. The reference EU Member State prepares a draft assessment and drafts of the related materials within 120 days after receipt of a valid application. The resulting assessment report is submitted to the concerned EU Member States which, within 90 days of receipt, must decide whether to approve the assessment report and related materials. If a concerned EU Member State cannot approve the assessment report and related materials due to concerns relating to a potential serious risk to public health, disputed elements may be referred to the European Commission, whose decision is binding on all EU Member States. In accordance with the mutual recognition procedure, the sponsor applies for national marketing authorization in one EU Member State. Upon receipt of this authorization the sponsor can then seek the recognition of this authorization by other EU Member States. Authorization in accordance with either of these procedures will result in authorization of the medicinal product only in the reference EU Member State and in the other concerned EU Member States.

A marketing authorization may be granted only to an applicant established in the EU. Regulation No. 1901/2006 provides that, prior to obtaining a marketing authorization in the EU, an applicant must demonstrate compliance with all measures included in a Pediatric Investigation Plan, or PIP, approved by the Pediatric Committee of the EMA, covering all subsets of the pediatric population, unless the EMA has granted a product-specific waiver, class waiver, or a deferral for one or more of the measures included in the PIP.

Orphan Drug Designation and Exclusivity in the EU

Regulation (EC) No 141/2000 and Regulation (EC) No. 847/2000 provide that a product can be designated as an orphan medicinal product by the European Commission if its sponsor can establish that the product is intended for the diagnosis, prevention or treatment of: (1) a life-threatening or chronically debilitating condition affecting not more than five in ten thousand persons in the EU when the application is made, or (2) a life-threatening, seriously debilitating or serious and chronic condition in the EU and that without incentives the medicinal product is unlikely to be developed. For either of these conditions, the applicant must demonstrate that there exists no satisfactory method of diagnosis, prevention or treatment of the condition in question that has been authorized in the EU or, if such method exists, the medicinal product will be of significant benefit to those affected by that condition.

Once authorized, orphan medicinal products are entitled to ten years of market exclusivity in all EU Member States and, in addition, a range of other benefits during the development and regulatory review process, including scientific assistance for trial protocols, authorization through the centralized marketing authorization procedure covering all member countries and a reduction or elimination of registration and marketing authorization fees. However, marketing authorization may be granted to a similar medicinal product with the same orphan indication during the ten year period with the consent of the marketing authorization holder for the

original orphan medicinal product or if the manufacturer of the original orphan medicinal product is unable to supply sufficient quantities. Marketing authorization may also be granted to a similar medicinal product with the same orphan indication if the product is safer, more effective or otherwise clinically superior to the original orphan medicinal product. The period of market exclusivity may, in addition, be reduced to six years if it can be demonstrated on the basis of available evidence that the original orphan medicinal product is sufficiently profitable not to justify maintenance of market exclusivity.

Pharmaceutical Coverage, Pricing and Reimbursement

In the United States and markets in other countries, patients who are prescribed treatments for their conditions and providers performing the prescribed services generally rely on third-party payors to reimburse all or part of the associated healthcare costs. Significant uncertainty exists as to the coverage and reimbursement status of products approved by the FDA and other government authorities. Thus, even if a product candidate is approved, sales of the product will depend, in part, on the extent to which third-party payors, including government health programs in the United States such as Medicare and Medicaid, commercial health insurers and managed care organizations, provide coverage, and establish adequate reimbursement levels for, the product. The process for determining whether a payor will provide coverage for a product may be separate from the process for setting the price or reimbursement rate that the payor will pay for the product once coverage is approved. Third-party payors are increasingly challenging the prices charged, examining the medical necessity, and reviewing the cost-effectiveness of medical products and services and imposing controls to manage costs. Third-party payors may limit coverage to specific products on an approved list, also known as a formulary, which might not include all of the approved products for a particular indication.

In order to secure coverage and reimbursement for any product that might be approved for sale, a company may need to conduct expensive pharmacoeconomic studies in order to demonstrate the medical necessity and cost-effectiveness of the product, in addition to the costs required to obtain FDA or other comparable marketing approvals. Nonetheless, product candidates may not be considered medically necessary or cost effective. A decision by a third-party payor not to cover a product candidate could reduce physician utilization once the product is approved and have a material adverse effect on sales, results of operations and financial condition. Additionally, a payor's decision to provide coverage for a product does not imply that an adequate reimbursement rate will be approved. Further, one payor's determination to provide coverage for a drug product does not assure that other payors will also provide coverage and reimbursement for the product, and the level of coverage and reimbursement can differ significantly from payor to payor.

The containment of healthcare costs also has become a priority of federal, state and foreign governments and the prices of drugs have been a focus in this effort. Governments have shown significant interest in implementing cost-containment programs, including price controls, restrictions on reimbursement and requirements for substitution of generic products. Adoption of price controls and cost-containment measures, and adoption of more restrictive policies in jurisdictions with existing controls and measures, could further limit a company's revenue generated from the sale of any approved products. Coverage policies and third-party reimbursement rates may change at any time. Even if favorable coverage and reimbursement status is attained for one or more products for which a company or its collaborators receive marketing approval, less favorable coverage policies and reimbursement rates may be implemented in the future.

Outside the United States, ensuring adequate coverage and payment for a product also involves challenges. Pricing of prescription pharmaceuticals is subject to governmental control in many countries. Pricing negotiations with governmental authorities can extend well beyond the receipt of regulatory marketing approval for a product and may require a clinical trial that compares the cost effectiveness of a product to other available therapies. The conduct of such a clinical trial could be expensive and result in delays in commercialization.

In the European Union, pricing and reimbursement schemes vary widely from country to country. Some countries provide that products may be marketed only after a reimbursement price has been agreed. Some countries may require the completion of additional studies that compare the cost-effectiveness of a particular drug candidate to currently available therapies or so called health technology assessments, in order to obtain reimbursement or pricing approval. For example, the European Union provides options for its member states to restrict the range of products for which their national health insurance systems provide reimbursement and to control the prices of medicinal products for human use. European Union member states may approve a specific price for a product or it may instead adopt a system of direct or indirect controls on the profitability of the company placing the product on the market. Other member states allow companies to fix their own prices for products, but monitor and control prescription volumes and issue guidance to physicians to limit prescriptions. Recently, many countries in the European Union have increased the amount of discounts required on pharmaceuticals and these efforts could continue as countries attempt to manage healthcare expenditures, especially in light of the severe fiscal and debt crises experienced by many countries in the European Union. The downward pressure on health care costs in general, particularly prescription drugs, has become intense. As a result, increasingly high barriers are being erected to the entry of new products. Political, economic and regulatory developments may further complicate pricing negotiations, and pricing negotiations may continue after reimbursement has been obtained. Reference pricing used by various European Union member states, and parallel trade, i.e., arbitrage between low-priced and high-priced member states, can further reduce prices. There can be no assurance that any

country that has price controls or reimbursement limitations for pharmaceutical products will allow favorable reimbursement and pricing arrangements for any products, if approved in those countries.

Healthcare Law and Regulation

Healthcare providers and third-party payors play a primary role in the recommendation and prescription of drug products that are granted marketing approval. Arrangements with providers, consultants, third-party payors and customers are subject to broadly applicable fraud and abuse, anti-kickback, false claims laws, reporting of payments to physicians and teaching physicians and patient privacy laws and regulations and other healthcare laws and regulations that may constrain business and/or financial arrangements. Restrictions under applicable federal and state healthcare laws and regulations, include the following:

- the federal Anti-Kickback Statute, which prohibits, among other things, persons and entities from knowingly and willfully soliciting, offering, paying, receiving or providing remuneration, directly or indirectly, in cash or in kind, to induce or reward either the referral of an individual for, or the purchase, order or recommendation of, any good or service, for which payment may be made, in whole or in part, under a federal healthcare program such as Medicare and Medicaid;
- the federal civil and criminal false claims laws, including the civil False Claims Act, and civil monetary penalties laws, which prohibit individuals or entities from, among other things, knowingly presenting, or causing to be presented, to the federal government, claims for payment that are false, fictitious or fraudulent or knowingly making, using or causing to made or used a false record or statement to avoid, decrease or conceal an obligation to pay money to the federal government.
- the federal Health Insurance Portability and Accountability Act of 1996, or HIPAA, which created additional federal criminal laws that prohibit, among other things, knowingly and willfully executing, or attempting to execute, a scheme to defraud any healthcare benefit program or making false statements relating to healthcare matters;
- HIPAA, as amended by the Health Information Technology for Economic and Clinical Health Act, and their respective implementing regulations, including the Final Omnibus Rule published in January 2013, which impose obligations, including mandatory contractual terms, with respect to safeguarding the privacy, security and transmission of individually identifiable health information;
- the federal false statements statute, which prohibits knowingly and willfully falsifying, concealing •or covering up a material fact or making any materially false statement in connection with the delivery of or payment for healthcare benefits, items or services;
- the federal transparency requirements known as the federal Physician Payments Sunshine Act, under the Patient Protection and Affordable Care Act, as amended by the Health Care Education Reconciliation Act, or the Affordable Care Act, which requires certain manufacturers of drugs, devices, biologics and medical supplies to report annually to the Centers for Medicare & Medicaid Services, or CMS, within the United States Department of Health and Human Services, information related to payments and other transfers of value made by that entity to physicians and teaching hospitals, as well as ownership and investment interests held by physicians and their immediate family members; and
- analogous state and foreign laws and regulations, such as state anti-kickback and false claims laws, which may apply to healthcare items or services that are reimbursed by third-party payors, including private insurers.

Some state laws require pharmaceutical companies to comply with the pharmaceutical industry’s voluntary compliance guidelines and the relevant compliance guidance promulgated by the federal government in addition to requiring drug manufacturers to report information related to payments and transfers of value to other health care providers and health care entities, or marketing expenditures. State and foreign laws also govern the privacy and security of health information in some circumstances, many of which differ from each other in significant ways and often are not preempted by HIPAA, thus complicating compliance efforts.

Healthcare Reform

A primary trend in the United States healthcare industry and elsewhere is cost containment. There have been a number of federal and state proposals during the last few years regarding the pricing of pharmaceutical and biopharmaceutical products, limiting coverage and reimbursement for drugs and other medical products, government control and other changes to the healthcare system in the United States.

In March 2010, the United States Congress enacted the Affordable Care Act, or the ACA, which, among other things, includes changes to the coverage and payment for products under government health care programs. In January 2017, Congress voted to adopt a budget resolution for fiscal year 2017, or the Budget Resolution, that authorizes the implementation of legislation that would repeal portions of the ACA. The Budget Resolution is not a law, however, it is widely viewed as the first step toward the passage of legislation that would repeal certain aspects of the ACA. Further, on January 20, 2017, President Trump signed an Executive Order

directing federal agencies with authorities and responsibilities under the ACA to waive, defer, grant exemptions from, or delay the implementation of any provision of the ACA that would impose a fiscal or regulatory burden on states, individuals, healthcare providers, health insurers, or manufacturers of pharmaceuticals or medical devices. Congress also could consider subsequent legislation to replace elements of the ACA that are repealed.

Other legislative changes have been proposed and adopted in the United States since the ACA was enacted. For example, in August 2011, the Budget Control Act of 2011, among other things, created measures for spending reductions by Congress. A Joint Select Committee on Deficit Reduction, tasked with recommending a targeted deficit reduction of at least $1.2 trillion for the years 2012 through 2021, was unable to reach required goals, thereby triggering the legislation's automatic reduction to several government programs. This includes aggregate reductions of Medicare payments to providers of up to 2% per fiscal year, which went into effect in April 2013 and will remain in effect through 2024 unless additional Congressional action is taken. In January 2013, President Obama signed into law the American Taxpayer Relief Act of 2012, which, among other things, further reduced Medicare payments to several providers, including hospitals, imaging centers and cancer treatment centers, and increased the statute of limitations period for the government to recover overpayments to providers from three to five years.

With the new Administration and Congress, there will likely be additional legislative changes, including repeal and replacement of certain provisions of the ACA. It remains to be seen, however, precisely what the new legislation will provide, when it will be enacted and what impact it will have on the availability of healthcare and containing or lowering the cost of healthcare.

Employees

As of December 31, 2016, we had 20 employees. 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 $23.7 million, $12.9 million and $38.3 million for the years ended December 31, 2016, 2015 and 2014, 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, 2016, we operate only in the United States.

Executive Officers of the Registrant

The following table lists the positions, names and ages of our executive officers as of March 17, 2017:

Executive Officers

Michael P. Bailey	51	Chief Executive Officer, President and Director
Keith S. Ehrlich	66	Chief Financial Officer
Michael N. Needle	57	Chief Medical Officer

Michael P. Bailey was appointed President and Chief Executive Officer and a member of our Board of Directors effective January 6, 2015. Mr. Bailey joined our company in September 2010 as our Chief Commercial Officer and was named our Chief Business Officer in June 2013. Prior to joining our company, Mr. Bailey served as Senior Vice President, Business Development and Chief Commercial Officer at Synta Pharmaceuticals Corp., a biopharmaceutical company focused on research, development and commercialization of oncology medicines, from 2008 to September 2010. From 1999 to 2008, Mr. Bailey worked at ImClone Systems Incorporated, a biopharmaceutical company focused on the development and commercialization of treatments for cancer patients. During his nine-year tenure at ImClone, he was responsible for commercial aspects of the planning and launch of ERBITUX® (cetuximab) across multiple oncology indications, as well as new product planning for the ImClone development portfolio, which included CYRAMZA® (ramucirumab) and PORTRAZZA® (necitumumab). In addition, Mr. Bailey was a key member of the strategic leadership committees for ImClone and its North American and worldwide partnerships and led 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., a biotechnology company, from 1997 to 1999. Mr. Bailey started his career in the

pharmaceutical industry as part of SmithKline 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 Mendoza College of Business at University of Notre Dame.

Keith S. Ehrlich, C.P.A. was appointed Chief Financial Officer in April 2015. Mr. Ehrlich served as a financial consultant to us from February 2015 to April 2015. Prior to joining our company, he worked with Synta Pharmaceuticals Corp. Mr. Ehrlich served as Synta's vice president of finance and administration from March 2004 until February 2015, and as its Chief Financial Officer from October 2006 to December 2014. Prior to Synta, Mr. Ehrlich served in various senior finance roles, including Chief Financial Officer of Argentys Corporation, Dyax Corp. and OraVax, Inc. Mr. Ehrlich also previously served as a director of finance at Vertex Pharmaceuticals, Inc. and as a senior audit manager with PricewaterhouseCoopers, LLP. Mr. Ehrlich received his B.A. in Biology from Drew University and his M.B.A. in Finance and Accounting from Rutgers University.

Michael N. Needle, M.D. was appointed Chief Medical Officer in January 2015. Dr. Needle has more than 15 years of pharmaceutical industry experience in drug development and regulatory affairs. This includes central roles in the development of oncology and hematology drugs, including Erbitux® (cetuximab), Revlimid® (lenalidomide) and Pomalyst® (pomolidimide). He most recently served as Chief Medical Officer for Array BioPharma Inc., a biopharmaceutical company, from April 2013 to September 2014. Prior to Array, Dr. Needle was Chief Medical Officer of the Multiple Myeloma Research Foundation and Consortium (MMRF), a research organization, from April 2012 to April 2013. From April 2010 to April 2012, Dr. Needle was Assistant Professor of Pediatrics at the College of Physicians and Surgeons of Columbia University. Previously, he held multiple Vice President level positions at Celgene Corporation, a biotechnology company, in Clinical Research and Development in Oncology, Strategic Medical Business Development, and Pediatric Strategy from March 2004 to April 2010. Dr. Needle also served as the Vice President of Clinical Affairs at ImClone from April 2000 to February 2004. Dr. Needle received his fellowship in Pediatric Hematology/Oncology at the Children's Hospital Medical Center, the Fred Hutchinson Cancer Research Center of the University of Washington in Seattle and the University of Texas M.D. Anderson Cancer Center in Houston. Dr. Needle has held faculty positions at the University of Pennsylvania and Columbia University. Dr. Needle graduated from Binghamton University with a Bachelor of Arts in Physics and received his medical degree from SUNY Downstate Medical Center, in Brooklyn, New York.

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 1 Broadway, 14th Floor, Cambridge, Massachusetts, 02142, and our telephone number is (617) 588-1960. 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.

We have adopted a code of business conduct and ethics, which applies to all of our officers, directors and employees, as well as charters for our audit committee, our compensation committee and our nominating and governance committee, and corporate governance guidelines. We have posted copies of our code of business conduct and ethics and corporate governance guidelines, as well as each of our committee charters, on the Corporate Governance page of the Investors section of our website, which you can access free of charge.

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.

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 Need for Additional Capital

We have identified conditions and events that raise substantial doubt about our ability to continue as a going concern.

We may be forced to delay or reduce the scope of our development programs and/or limit or cease our operations if we are unable to raise substantial additional funding to meet our future working capital needs and maintain compliance with our $10.0 million financial covenant under our loan agreement with Hercules. We believe that our approximate $23.3 million in cash, cash equivalents and marketable securities at December 31, 2016, could allow us to fund our planned operations into the fourth quarter of 2017; however, additional funds will be needed to extend these operations into 2018 and maintain compliance with our financial covenant. However, we cannot guarantee that we will be able to obtain sufficient additional funding when needed or that such funding, if available, will be obtainable on terms satisfactory to us. In the event that these plans cannot be effectively realized, there can be no assurance that we will be able to continue as a going concern.

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

We have incurred net losses of $26.9 million, $15.0 million and $52.7 million for the fiscal years ended December 31, 2016, 2015 and 2014, respectively. As of December 31, 2016, we had an accumulated deficit of $521.9 million. To date, we have not commercialized any products or generated any revenues from the sale of products, and absent the realization of sufficient revenues from product sales, we may never attain profitability. 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 product candidates. As noted above, we and our auditors have identified conditions and events that raise substantial doubt about our ability to continue as a going concern.

If we do not successfully develop and obtain regulatory approval for our existing and future pipeline of product candidates and effectively manufacture, market and sell any product candidates that are approved, we may never generate product sales. 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.

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

We will require substantial additional funds to continue our development programs and to fulfill our planned operating goals. In particular, our currently planned operating and capital requirements include the need for substantial working capital to support our development activities for tivozanib. For example, we estimate that the remaining costs

for the TIVO-3 trial for RCC, including drug supply and distribution, could be in the range of $22.0 million to $25.0 million in the aggregate through 2018. We have also initiated the TiNivo trial in collaboration with BMS, which is providing nivolumab for the study. We are the trial sponsor. The TiNivo trial is a phase 1/2 clinical trial of tivozanib combined with nivolumab, a PD-1 inhibitor, for the treatment of patients with RCC for which our costs, including tivozanib drug supply and distribution, could be in the range of $2.0 million to $2.5 million through 2018. Moreover, we have future payment obligations and cost-sharing arrangements under certain of our collaboration and license agreements. For example, under our agreements with KHK and St. Vincent's, we are required to make certain clinical and regulatory milestone payments, have royalty obligations with respect to product sales and are required to pay a portion of sublicense revenue in certain instances.

We are party to a loan and security agreement with a third party, Hercules, that includes a financial covenant that requires us to maintain an unrestricted cash position (defined as cash and liquid cash, including marketable securities) greater than or equal to $10.0 million through the date of completion of our Phase 3 TIVO-3 trial. Non-compliance with the financial covenant under the loan and

security agreement with Hercules would be considered an event of default that could result in Hercules, at its option, accelerating and demanding payment of all outstanding obligations together with a prepayment charge.

Based upon our approximate $23.3 million in existing cash, cash equivalents and marketable securities as of December 31, 2016 and the $10.0 million financial covenant under the Loan Agreement with Hercules, we do not have sufficient cash on hand to support operations and maintain compliance with the $10.0 million financial covenant under our loan agreement with Hercules for at least the next twelve months from the date of filing of this Annual Report on Form-10K. These conditions and events raise substantial doubt about our ability to continue as a going concern. Moreover, we believe that our approximate $23.3 million in cash, cash equivalents and marketable securities at December 31, 2016 could allow us to fund our planned operations into the fourth quarter of 2017. This estimate assumes no receipt of milestone payments from our partners or related payment of potential licensing milestones to third parties, no additional funding from new partnership agreements, no equity financings, no debt financings, no accelerated repayment of our term loan and no further sales of equity under our sales agreement with FBR. Accordingly, the timing and nature of activities contemplated for 2017 and thereafter will be conducted subject to the availability of sufficient financial resources.

Furthermore, there are numerous risks and uncertainties associated with research, development and commercialization of pharmaceutical products. Accordingly, our future capital requirements may vary from our current expectations and depend on many factors, including but not limited to:

- our ability to establish and maintain strategic partnerships, licensing or other arrangements and the financial terms of such agreements;
- the number and characteristics of the product candidates we pursue;
- the scope, progress, results and costs of developing our product candidates and of conducting preclinical and clinical trials;
- the timing of, and the costs involved in, obtaining regulatory approvals for our product candidates;
- the costs involved in preparing, filing, prosecuting, maintaining, defending and enforcing patent claims, including litigation costs and the outcome of such litigation;
- the absence of any breach, acceleration event or event of default under our loan agreement with Hercules or under any other agreements with third parties;
- the outcome of legal actions against us, including the current lawsuits described in Part I, Item 3 of this report under the heading “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;
- the timing, receipt and amount of sales of, or royalties on, our future products, if any; and
- our ability to continue as a going concern.

We will require additional funding to extend our planned operations into 2018 and maintain compliance with our financial covenant under our loan agreement with Hercules. 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. Additional funds may not be available when we need them, on terms that are acceptable to us, or at all. We also expect to seek additional funds through arrangements with collaborators, licensees or other third parties. These arrangements would generally require us to relinquish or encumber rights to some of our technologies or drug candidates, and we may not be able to enter into such arrangements on acceptable terms, if at all.

If we are unable to raise substantial additional capital in the near term, whether on terms that are acceptable to us, or at all then we would trigger an event of default under our loan agreement with Hercules and we may be required to:

- delay, limit, reduce or terminate our clinical trials or other 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 are a development stage company, 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 the development stage. 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 10 to 15 years to develop one new medicine from the time it is discovered to when it is available for treating patients. Preclinical studies and clinical trials may involve 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. 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 a development stage business, we may encounter unforeseen expenses, difficulties, complications, delays and other known and unknown factors. To be profitable, we will need to transition from a company with a research and development focus to a company capable of supporting commercial activities. We may not be successful in such a transition.

Risks Related to our Litigation

We and certain of our former officers and present and former directors have been named as defendants in multiple lawsuits that could result in substantial costs and divert management's attention.

We, and certain of our former officers and directors, were named as defendants in a consolidated class action lawsuit initiated in 2013 that generally alleges that we and those individuals violated federal securities laws by making allegedly false and/or misleading statements in 2012 and 2013, concerning the development of our drug tivozanib and its prospects for FDA approval at that time. The lawsuit seeks unspecified damages, interest, attorneys' fees, and other costs. The consolidated amended complaint was dismissed without prejudice on March 20, 2015, and the lead plaintiffs then filed a second amended complaint bringing similar allegations. This second amended complaint was dismissed with prejudice on November 18, 2015. The lead plaintiffs appealed the court's decision to the United States Court of Appeals for the First Circuit and also filed a motion to vacate and reconsider the district court's judgment, which we opposed. On January 3, 2017, the Court granted Plaintiffs' motion to vacate the dismissal and judgment and Plaintiffs filed a motion to dismiss their appeal on February 8, 2017. On February 2, 2017, Plaintiffs filed a third amended complaint alleging claims similar to those alleged in the prior complaints, namely that we and certain of our 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 clinical trial in an effort to lead investors to believe that the drug would receive approval from the FDA. On March 2, 2017, we filed an answer to the third amended complaint, and the parties have initiated discovery. The lawsuit seeks unspecified damages, interest, attorneys' fees, and other costs. Another plaintiff has also filed a derivative complaint, allegedly on our behalf, naming us as a nominal defendant and also naming as defendants present and former members of our board of directors, alleging breach of fiduciary duty and abuse of control on the part of those directors with respect to the same statements at issue in the securities litigation. 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. The derivative complaint was dismissed with prejudice on March 18, 2015. The plaintiff has appealed the court's decision to the United States Court of Appeals for the First Circuit. The parties have reached an agreement in principle to settle this matter. The settlement involves certain corporate governance changes and other non-monetary relief. The plaintiff is seeking an award of attorney's fees, costs, and expenses in the amount of $822,116, as well as an incentive award of $2,500, both of which we expect will be paid by insurance in the amount ordered by the Court. On September 16, 2016, the Court granted preliminary approval to the proposed settlement. On December 19, 2016, the Court held a final settlement hearing on the terms of the proposed settlement and to consider the award of fees to the plaintiff's attorneys. No objections to the settlement were filed with

the Court or raised at the hearing. At the hearing, the Court indicated orally that the settlement will be approved, and heard argument regarding the size of plaintiff's potential attorney's fee award. A formal approval order has not yet entered and the Court has not ruled on the final amount of fees for the plaintiff's attorneys (which, as stated above, are expected to be paid by insurance). Until a formal approval order has been entered, there can be no complete assurance that the Court will approve the settlement.

We intend to continue to deny the allegations in the class action case and to engage in a vigorous defense of such lawsuit. We intend to resolve the derivative lawsuit in accordance with the proposed settlement. 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 could have a material adverse effect on our financial condition and business. For example, we could incur substantial costs not covered by our 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 liability insurance, which could have a material adverse effect on our operating results or financial condition.

We have concluded a settlement with the SEC, but the SEC is still pursuing an action against our former officers.

We paid $4.0 million to settle a lawsuit filed by the SEC in federal court alleging that we violated federal securities laws by omitting to disclose the recommendation of the staff of the U.S. Food and Drug Administration, on May 11, 2012, that we conduct an additional clinical trial with respect to tivozanib. See Part I, Item 3 of this report under the heading "Legal Proceedings" for a further discussion of these claims. The SEC also named three of our former officers as defendants in the same lawsuit, and those claims are still pending. We are not a party to the continuing litigation between the SEC and the former officers. However, those individuals have and may continue to seek advancement of legal expenses or indemnification for any losses, either of which could be material to the extent not covered by our director and officer liability insurance.

Risks Related to Development and Commercialization of Our Drug Candidates

In the near term, we are substantially dependent on the success of tivozanib. If we are unable to complete the clinical development of, obtain marketing approval for or successfully commercialize tivozanib, either alone or with our collaborators, or if we experience significant delays in doing so, our business could be substantially harmed.

We currently have no products approved for sale and are investing a significant portion of our efforts and financial resources in the development of tivozanib for marketing approval in North America. Our prospects are substantially dependent on our ability to develop, obtain marketing approval for and successfully commercialize tivozanib in one or more disease indications.

The success of tivozanib will depend on a number of factors, including the following:

- our ability to secure the substantial additional capital required to complete our clinical trials of tivozanib, including the TIVO-3 trial and the TiNivo trial;
- successful enrollment and completion of clinical trials;
    - a safety, tolerability and efficacy profile that is satisfactory to the FDA, EMA or any other comparable foreign regulatory authority for marketing approval;
- timely receipt of marketing approvals from applicable regulatory authorities;
- the performance of our collaborators and third-party contractors;
    - the extent of any required post marketing approval commitments to applicable regulatory authorities;
- maintenance of existing or establishment of new supply arrangements with third party raw materials suppliers and manufacturers including with respect to the supply of active pharmaceutical ingredient for tivozanib and finished drug product that is appropriately packaged for sale;
- adequate ongoing availability of raw materials and drug product for clinical development and any commercial sales;
- obtaining and maintaining patent, trade secret protection and regulatory exclusivity, both in the United States and internationally, including our ability to maintain our license agreement with KHK;
- protection of our rights in our intellectual property portfolio, including our ability to maintain our license agreement with KHK;
- successful launch of commercial sales following any marketing approval;
- a continued acceptable safety profile following any marketing approval;
- commercial acceptance by patients, the medical community and third party payors;
- successful identification of biomarkers for patient selection; and
- our ability to compete with other therapies.

Many of these factors are beyond our control, including clinical trial results, the regulatory approval process, potential threats to our intellectual property rights and the development, manufacturing, marketing and sales efforts of our collaborators. If we are unable to develop, receive marketing approval for and successfully commercialize tivozanib

on our own or with our collaborators, or experience delays as a result of any of these factors or otherwise, our business could be substantially harmed.

If clinical trials of any product candidates that we or our collaborators may develop fail to satisfactorily demonstrate safety and efficacy to the FDA and other regulators, we or our collaborators may incur additional costs or delays, or may be unable to complete, the development and commercialization of these product candidates.

We, and any collaborators, including our partners and sublicensees, are not permitted to commercialize, market, promote or sell any product candidate in the United States without obtaining marketing approval from the FDA. Foreign regulatory authorities, such as the EMA, impose similar requirements. We and our collaborators must complete extensive preclinical development and clinical trials that demonstrate the safety and efficacy of our product candidates in humans before we can obtain these approvals.

Clinical testing is expensive, is difficult to design and implement, and can take many years to complete. It is inherently uncertain as to outcome. We cannot guarantee that any clinical trials will be conducted as planned or completed on schedule, if at all. The clinical development of our product candidates is susceptible to the risk of failure inherent at any stage of product development, as well as failure to demonstrate efficacy at all in a clinical trial or across a broad population of patients, the occurrence of adverse events that are medically severe or commercially unacceptable, failure to comply with protocols or regulatory requirements and determination by the applicable regulatory authority that a product candidate may not continue development or is not approvable. Even if a product candidate has a beneficial effect, that effect may not be detected during clinical evaluation due to a variety of factors, including the size, duration, design, measurements, conduct or analysis of our clinical trials. Conversely, as a result of the same factors, our clinical trials may indicate an apparent positive effect of a product candidate that is greater than the actual positive effect, if any. Similarly, in our clinical trials we may fail to detect toxicity or intolerability of our product candidates, or mistakenly believe that our product candidates are toxic or not well tolerated when that is not in fact the case.

Any inability to timely or successfully complete preclinical and clinical development could result in additional unplanned costs and impair our ability to generate revenues from product sales, regulatory and commercialization milestones and royalties. Moreover, if we, or any collaborators, are required to conduct additional clinical trials or other testing of our product candidates beyond those planned, or if the results of these trials or tests are unfavorable, uncertain, only modestly favorable or indicate safety concerns, we or our collaborators, may:

- be delayed in obtaining marketing approval for our product candidates;
- not obtain marketing approval at all;
- obtain approval for indications or patient populations that are not as broad as intended or desired;
- obtain approval with labeling that includes significant use or distribution restrictions or significant safety warnings, including boxed warnings;
- be subject to additional post marketing testing or other requirements; or
- be required to remove the product from the market after obtaining marketing approval.

Our failure to successfully complete clinical trials of our product candidates and to demonstrate the efficacy and safety necessary to obtain regulatory approval would significantly harm our business.

Adverse events or undesirable side effects caused by, or other unexpected properties of, tivozanib or our other product candidates may be identified during development and could delay or prevent their marketing approval or limit their use.

Adverse events or undesirable side effects caused by, or other unexpected properties of, tivozanib or our other product candidates could cause us, any collaborators, an institutional review board or regulatory authorities to interrupt, delay or halt clinical trials of one or more of our product candidates and could result in a more restrictive label or the delay or denial of marketing approval by the FDA or comparable foreign regulatory authorities. If any of our product candidates is associated with adverse events or undesirable side effects or has properties that are unexpected, we, or any collaborators, may need to abandon development or limit development of that product candidate to certain uses or subpopulations in which the undesirable side effects or other characteristics are less prevalent, less severe or more

acceptable from a risk benefit perspective. Many compounds that initially showed promise in clinical or earlier stage testing have later been found to cause side effects that prevented further development of the compound.

If we or our collaborators experience any of a number of possible complications in connection with preclinical or clinical trials of our product candidates, potential clinical development, marketing approval or commercialization of our product candidates could be delayed or prevented.

We or our collaborators may experience numerous complications in connection with preclinical or clinical trials that could delay or prevent clinical development, marketing approval or commercialization of our product candidates including:

- regulators or institutional review boards may not authorize us, any collaborators or our or their investigators to commence a clinical trial or conduct a clinical trial at a prospective trial site;
- delay or failure to reach agreement on clinical trial contracts or clinical trial protocols with prospective trial sites;
- unfavorable or inconclusive clinical trial results;
- our decision or a regulatory order to conduct additional clinical trials or abandon product development programs;
- the number of patients required for our clinical trials may be larger than anticipated, patient enrollment may be slower than anticipated or participants may drop out of these clinical trials at a higher rate than anticipated;
- the costs of our clinical trials may be greater than we anticipate;
- our third party contractors, including those manufacturing our product candidates, or conducting clinical trials on our behalf, may fail to successfully comply with regulatory requirements or meet their contractual obligations in a timely manner or at all;
- patients that enroll in a clinical trial may misrepresent their eligibility to do so or may otherwise not comply with the clinical trial protocol, resulting in the need to drop the patients from the clinical trial, increase the needed enrollment size for the clinical trial or extend the clinical trial's duration;
- We may decide, or regulators or institutional review boards may require that we suspend or terminate clinical research for various reasons, including noncompliance with regulatory requirements or their standards of conduct, a finding that the participants are being exposed to unacceptable health risks, undesirable side effects or other unexpected characteristics of the product candidate or findings of undesirable effects caused by a chemically or mechanistically similar product or product candidate;
- the FDA or comparable foreign regulatory authorities may disagree with our or our collaborators' clinical trial designs or interpretation of data from preclinical studies and clinical trials;
- the FDA or comparable foreign regulatory authorities may fail to approve or subsequently find fault with the manufacturing processes or facilities of third party manufacturers with which we, or any collaborators, enter into agreements for clinical and commercial supplies;
- the supply or quality of raw materials or manufactured product candidates or other materials necessary to conduct clinical trials of our product candidates may be insufficient, inadequate or not available at an acceptable cost, or we may experience interruptions in supply; and
- the approval policies or regulations of the FDA or comparable foreign regulatory authorities may significantly change in a manner rendering our clinical data insufficient to obtain marketing approval.

Product development costs for us and our collaborators will increase if we experience delays in testing or pursuing marketing approvals, and we may be required to obtain additional funds to complete clinical trials and prepare for possible commercialization. We do not know whether any trials will begin as planned, will need to be restructured, or will be completed on schedule or at all. Significant clinical trial delays also could shorten any periods during which we may have the exclusive right to commercialize our product candidates or allow our competitors to bring products to market before we do could impair our ability to successfully commercialize our product candidates and may harm our business and results of operations. In addition, many of the factors that lead to clinical trial delays may ultimately lead to the denial of marketing approval of any of our product candidates.

If we or our collaborators experience delays or difficulties in the enrollment of patients in clinical trials, receipt of necessary regulatory approvals could be delayed or prevented.

We or our collaborators may not be able to initiate or continue clinical trials for our product candidates if we are unable to locate and enroll a sufficient number of eligible patients to participate in clinical trials. Patient enrollment is a significant factor in the timing of clinical trials, and is affected by many factors, including:

- the size and nature of the patient population;
- the severity of the disease under investigation;
- the availability of approved therapeutics for the relevant disease;
- the proximity of patients to clinical sites;
- the eligibility criteria for the trial;
- the design of the clinical trial;
- efforts to facilitate timely enrollment;
- competing clinical trials; and
- clinicians' and patients' perceptions as to the potential advantages and risks of the drug being studied and the drug being provided as a control in relation to other available therapies, including any new drugs that may be approved for the indications we are investigating.

Our inability to enroll a sufficient number of patients for our clinical trials could result in significant delays or may require us to abandon one or more clinical trials altogether. Enrollment delays in our clinical trials may result in increased development costs for our product candidates, delay or halt the development of and approval processes for our product candidates and jeopardize our ability to commence sales of and generate revenues from our product candidates, which could cause the value of our company to decline and limit our ability to obtain additional financing, if needed.

Results of early clinical trials may not be predictive of results of late stage clinical trials.

The outcome of early clinical trials may not be predictive of the success of later clinical trials, and interim results of clinical trials do not necessarily predict success in future clinical trials. Many companies in the pharmaceutical and biotechnology industries have suffered significant setbacks in late stage clinical trials after achieving positive results in earlier development, and we have and could, in the future, face similar setbacks. For example, in June 2013, the FDA issued a response letter informing us that it would not approve tivozanib for the treatment of first-line advanced renal cell carcinoma based solely on the data from TIVO-1, our initial phase 3 trial, and recommended that we perform an additional clinical trial that is adequately sized to assure the FDA that there is no adverse effect on overall survival.

The design of a clinical trial can determine whether its results will support approval of a product, and flaws in the design of a clinical trial may not become apparent until the clinical trial is well advanced. We have limited experience in designing clinical trials and may be unable to design and execute a clinical trial to support marketing approval. In addition, preclinical and clinical data are often susceptible to varying interpretations and analyses. Many companies that believed their product candidates performed satisfactorily in preclinical studies and clinical trials have nonetheless failed to obtain marketing approval for the product candidates. Even if we, or any collaborators, believe that the results of clinical trials for our product candidates warrant marketing approval, the FDA or comparable foreign regulatory authorities may disagree and may not grant marketing approval of our product candidates.

In some instances, there can be significant variability in safety or efficacy results between different clinical trials of the same product candidate due to numerous factors, including changes in trial procedures set forth in protocols, differences in the size and type of the patient populations, changes in and adherence to the dosing regimen and other clinical trial protocols and the rate of dropout among clinical trial participants. If we fail to receive positive results in clinical trials of our product candidates, the development timeline and regulatory approval and commercialization prospects for our most advanced product candidates, and, correspondingly, our business and financial prospects would be negatively impacted.

We have never obtained marketing approval for a product candidate, and we may never obtain marketing approval for our product candidates.

We have never obtained marketing approval for a product candidate. It is possible that the FDA, the EMA or any other comparable foreign regulatory agency may refuse to accept for substantive review any future application that we or a collaborator may submit to market and sell our product candidates, or that any such agency may conclude after review of our or our collaborator’s data

that such application is insufficient to obtain marketing approval of our product candidate. For example, our TIVO-1 trial met its primary endpoint for progression-free survival, or PFS, but showed a non-statistically significant trend favoring the control arm in overall survival, or OS. In June 2013, the FDA issued a complete response letter informing us that it would not approve tivozanib for the first-line treatment of advanced RCC based solely on the data from the TIVO-1 trial, and recommended that we perform an additional clinical trial adequately sized to assure the FDA that there is no adverse effect on OS.

Subsequently, EUSA, our licensee, submitted a MAA for tivozanib for the treatment of RCC with the EMA in February 2016 based primarily on our existing dataset, which includes the results from the TIVO-1 trial combined with the TIVO-1 extension trial, and one phase 1 and two phase 2 trials in RCC. The EMA validated the MAA in March 2016, confirming that the submission was complete and that it would initiate its review process. EUSA received the Day 120 List of Questions from the CHMP of the EMA in July 2016, and submitted its responses in November 2016. In January 2017, EUSA received the Day 180 LOI from the CHMP. The Day 180 LOI signifies that the MAA for tivozanib is not approvable at the present time, and outlines outstanding deficiencies, which are then required to be satisfactorily addressed in an oral explanation and/or in writing prior to a final application decision. EUSA has informed us that it expects to submit written responses to the Day 180 LOI in April 2017, and the EMA has tentatively scheduled EUSA to provide an oral explanation to the CHMP in May 2017. We cannot predict the outcome of EUSA's MAA submission to the EMA for tivozanib.

If the FDA, EMA or any other foreign regulatory agency does not accept or approve any application to market and sell any of our product candidates, such agency may require that we conduct additional clinical trials, preclinical studies or manufacturing validation studies and submit that data before it will reconsider our application. Depending on the extent of these or any other required trials or studies, approval of any application that we submit may be delayed by several years, or may require us or our collaborator to expend more resources than we or they have available. It is also possible that additional trials or studies, if performed and completed, may not be considered sufficient by the FDA, EMA or any other regulatory agency to approve our applications for marketing and commercialization.

Any delay in obtaining, or an inability to obtain, marketing approvals would prevent us or our collaborators from commercializing our product candidates and generating revenues. If any of these outcomes occur, we would not be eligible for milestone and royalty revenue under our partnership agreements, our collaborators could terminate our partnership agreements, and we may be forced to abandon our development efforts for our product candidates, which could significantly harm our business.

Even if a product candidate receives marketing approval, we or others may later discover that the product is less effective than previously believed or causes undesirable side effects that were not previously identified, which could compromise our ability, or that of any collaborators, to market the product.

Clinical trials of our product candidates will be conducted in carefully defined subsets of patients who have agreed to participate in these. Consequently, it is possible that our clinical trials may indicate an apparent positive effect of a product candidate that is greater than the actual positive effect, if any, or alternatively fail to identify undesirable side effects. If, following approval of a product candidate, we, or others, discover that the product is less effective than previously believed or causes undesirable side effects that were not previously identified, any of the following adverse events could occur:

- regulatory authorities may withdraw their approval of the product or seize the product;
- we may be required to recall the product, change the way the product is administered or conduct additional clinical trials;
- additional restrictions may be imposed on the marketing of, or the manufacturing processes for, the particular product;
- we may be subject to fines, injunctions or the imposition of civil or criminal penalties;

- regulatory authorities may require the addition of labeling statements, such as a “black box” warning or a contraindication;
- we may be required to create a Medication Guide outlining the risks of the previously unidentified side effects for distribution to patients;
- we could be sued and held liable for harm caused to patients;
- physicians and patients may stop using our product; and
- our reputation may suffer.

Any of these events could harm our business and operations, and could negatively impact our stock price.

Even if our product candidates receive marketing approval, they may fail to achieve the degree of market acceptance by physicians, patients, third party payors and others in the medical community necessary for commercial success, in which case we may not generate significant revenues or become profitable.

We have never commercialized a product, and even if one of our product candidates is approved by the appropriate regulatory authorities for marketing and sale, it may nonetheless fail to gain sufficient market acceptance by physicians, patients, third party payors and others in the medical community. Physicians are often reluctant to switch their patients from existing therapies even when new and potentially more effective or convenient treatments enter the market. Further, patients often acclimate to the therapy that they are currently taking and do not want to switch unless their physicians recommend switching products or they are required to switch therapies due to lack of reimbursement for existing therapies.

Efforts to educate the medical community and third party payors on the benefits of our product candidates may require significant resources and may not be successful. If any of our product candidates is approved but does not achieve an adequate level of market acceptance, we may not generate significant revenues and we may not become profitable. The degree of market acceptance of our product candidates, if approved for commercial sale, will depend on a number of factors, including:

- the efficacy and safety of the product;
- the advantages of the product compared to competitive therapies;
- the number of competitors approved for similar uses;
- the relative promotional effort of us as compared with our competitors;
- the prevalence and severity of any side effects;
- whether the product is designated under physician treatment guidelines as a first , second or third line therapy;
- our ability to offer the product for sale at competitive prices;
- the product's convenience and ease of administration compared to alternative treatments;
- the willingness of the target patient population to try, and of physicians to prescribe, the product;
- limitations or warnings, including distribution or use restrictions, contained in the product's approved labeling;
- the strength of sales, marketing and distribution support;
- changes in the standard of care for the targeted indications for the product; and
- availability and amount of coverage and reimbursement from government payors, managed care plans and other third party payors.

If we are unable to establish sales, marketing and distribution capabilities or enter into sales, marketing and distribution arrangements with third parties, we may not be successful in commercializing any product candidates if approved.

We do not have sales, marketing or distribution infrastructure and have no experience as an organization in the sale, marketing or distribution of pharmaceutical products. To achieve commercial success for any approved product, we must either develop a sales and marketing organization or outsource these functions to third parties. The development of sales, marketing and distribution capabilities will require substantial resources, will be time consuming and, if not initiated sufficiently in advance of marketing approval, could delay any product launch. Conversely, the commercial launch of a product candidate for which we recruit a sales force and establish marketing and distribution capabilities is delayed or does not occur for any reason, we could incur substantial costs and our investment could be lost if we cannot retain or reposition our sales and marketing personnel. In addition, we may not be able to hire or retain a sales force in the United States that is sufficient in size or has adequate expertise in the medical markets that we plan to target. If we are unable to establish or retain a sales force and marketing and distribution capabilities, our operating results may be adversely affected.

If we enter into arrangements with third parties to perform sales, marketing and distribution services, our product revenues or the profitability of these product revenues may be substantially lower than if we were to directly market and sell products in those markets. Furthermore, we may be unsuccessful in entering into the necessary arrangements

with third parties or may be unable to do so on terms that are favorable to us. In addition, we may have little or no control over such third parties, and any of them may fail to devote the necessary resources and attention to sell and market our products effectively.

We may seek to enter into collaborations that we believe may contribute to our ability to advance development and ultimately commercialize our product candidates. We also seek to enter into collaborations where we believe that realizing the full commercial value of our development programs will require access to broader geographic markets or the pursuit of broader patient populations or

indications. If a potential partner has development or commercialization expertise that we believe is particularly relevant to one of our products, then we may seek to collaborate with that potential partner even if we believe we could otherwise develop and commercialize the product independently.

If we do not establish sales, marketing and distribution capabilities, either on our own or in collaboration with third parties, we will not be successful in commercializing any of our product candidates that receive marketing approval.

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, in collaboration with a third party, 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 or our collaborators 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. 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. We expect to rely in part on third parties for the design, development and manufacture of any companion diagnostic. 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.

We face substantial competition from existing approved products. Our competitors may also discover, develop or commercialize new competing products before, or more successfully, than we do.

The biotechnology and pharmaceutical industries are highly competitive. 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 will compete with existing, market-leading products.

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, but not limited to, Actelion Pharmaceuticals Ltd., Amgen, Inc., Arqule, Inc., AstraZeneca, Bayer HealthCare AG, Bristol-Myers Squibb, Eisai Co., Ltd., Eli Lilly and Company, Exelixis, Inc., Gilead Sciences, Inc., GlaxoSmithKline plc, GTx, Inc., Helsinn and XBiotech, Incyte Corporation, Janssen Pharmaceuticals, Inc. (a division of Johnson and Johnson), Jazz Pharmaceuticals plc, Merck, Merrimack Pharmaceuticals, Inc., Novartis, OncoMed Pharmaceuticals, Inc., Pfizer Inc., Roche Laboratories, Inc., and United Therapeutics Corporation are pursuing the development or are currently marketing pharmaceuticals that target VEGF, HGF, ErbB3, Notch 3 or other pathways on which we may focus, as well as cachexia. It is probable that the number of companies seeking to develop competing products and therapies 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 product discovery and development, obtaining FDA and other

regulatory approvals, and commercialization. Many are already marketing products to treat the same indications, and having the same biological targets, as the product candidates we are developing, including with respect to renal cell carcinoma. 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, develop and commercialize products that are superior to other products in the market in terms of, among other things, safety, efficacy, convenience, or price;
- 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 our products.

Established competitors may invest heavily to 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, our business will not grow and our financial condition and operations will suffer.

There are currently 11 FDA-approved drugs in oncology which, like tivozanib, target the VEGF pathway as a part or all of their inhibitory mechanism. Eight of the FDA-approved VEGF pathway inhibitors are oral small molecule receptor tyrosine kinase inhibitors, or TKIs. Many of the approved VEGF pathway inhibitors are in ongoing development in additional cancer indications including RCC. Additionally, we are aware of a number of companies that have ongoing programs to develop both small molecules and biologics that target the VEGF pathway. The emergence of PD-1/PD-L1 inhibitor and other immune system-targeted therapies present additional competition for tivozanib in advanced RCC, and clinical trials for mono and combination therapies of PD-1/PD-L1 with other immune-oncology targets and VEGF TKIs targeting RCC are in the pipeline. We are aware of several ongoing phase 3 registration studies evaluating PD-1/PD-L1 inhibitors in combination with VEGF TKIs in RCC, as well as combinations of PD-1 agents in combination with other immune therapies for RCC.

We believe the products that are considered competitive with ficlatuzumab include those agents targeting the HGF/c-Met pathway. We believe the most direct competitors to our AV-203 program are monoclonal antibodies that specifically target the ErbB3 receptor. There are also other agents that target ErbB3 as a part or all of their inhibitory mechanism. Only a limited number of agents have been approved for the treatment or prevention of cachexia caused by any disease. A number of agents with different mechanisms of action, however, have completed or are currently being studied in phase 2 trials in cachexia or muscle wasting. Currently, there are no ongoing clinical trials of Notch 3-specific inhibitors or any approved Notch 3-specific inhibitors in PAH patients; however, there are multiple treatments approved for PAH through various mechanisms.

Even if we or our collaborators are able to commercialize any product candidate, the product may become subject to unfavorable pricing regulations, third party payor reimbursement practices or healthcare reform initiatives, any of which could harm our business.

The commercial success of our product candidates will depend substantially, both domestically and abroad, on the extent to which the costs of our product candidates will be paid by third party payors, including government health care programs and private health insurers. If coverage is not available, or reimbursement is limited, we, or any collaborators, may not be able to successfully commercialize our product candidates. Even if coverage is provided, the approved reimbursement amount may not be high enough to allow us or our collaborators to establish or maintain pricing sufficient to realize a sufficient return on our investments. In the United States, no uniform policy of coverage and reimbursement for products exists among third party payors, and coverage and reimbursement levels for products can differ significantly from payor to payor. As a result, the coverage determination process is often time consuming and costly and may require us to provide scientific and clinical support for the use of our products to each payor separately, with no assurance that coverage and adequate reimbursement will be obtained or applied consistently.

There is significant uncertainty related to third party payor coverage and reimbursement of newly approved drugs. Marketing approvals, pricing and reimbursement for new drug products vary widely from country to country. Some countries require approval of the sale price of a drug before it can be marketed. In many countries, the pricing review period begins after marketing or product licensing approval is granted. In some foreign markets, prescription pharmaceutical pricing remains subject to continuing governmental control even after initial approval is granted. As a result, we or our collaborators might obtain marketing approval for a product in a particular country, but then be subject to price regulations that delay commercial launch of the product, possibly for lengthy time periods, which may negatively impact the revenues we are able to generate from the sale of the product in that country. Adverse pricing limitations may hinder our ability to recoup our or their investment in one or more product candidates, even if our product candidates obtain marketing approval.

Patients who are provided medical treatment for their conditions generally rely on third party payors to reimburse all or part of the costs associated with their treatment. Therefore, our ability, and the ability of any collaborators, to commercialize successfully any of our product candidates will depend in part on the extent to which coverage and adequate reimbursement for these products and related treatments will be available from third party payors. Third party payors decide which medications they will cover and establish reimbursement levels. The healthcare industry is acutely focused on cost containment, both in the United States and elsewhere. Government authorities and other third party payors have attempted to control costs by limiting coverage and the amount of reimbursement for particular medications, which could affect our ability to sell our product candidates profitably. These payors may not view our products, even if approved, as cost effective, and coverage and reimbursement may not be available to our customers or may not be sufficient to allow our products to be marketed on a competitive basis. Cost control initiatives could cause us or our collaborators to decrease the price we might establish for products, which could result in lower than anticipated product revenues. If the prices for our products, if any, decrease or if governmental and other third party payors do not provide coverage or adequate reimbursement, our prospects for revenue and profitability will suffer.

There may also be delays in obtaining coverage and reimbursement for newly approved drugs, and coverage may be more limited than the indications for which the drug is approved by the FDA or comparable foreign regulatory authorities. Moreover, eligibility for reimbursement does not imply that any drug will be paid for in all cases or at a rate that covers our costs, including research, development, manufacture, sale and distribution. Reimbursement rates may vary, for example, according to the use of the product and the clinical setting in which it is used. Reimbursement rates may also be based on reimbursement levels already set for lower cost drugs or may be incorporated into existing payments for other services.

In addition, increasingly, third party payors are requiring higher levels of evidence of the benefits and clinical outcomes of new technologies and are challenging the prices charged. Further, the net reimbursement for drug products may be subject to additional reductions if there are changes to laws that presently restrict imports of drugs from countries where they may be sold at lower prices than in the United States. An inability to promptly obtain coverage and adequate payment rates from both government funded and private payors for any of our product candidates for which we obtain marketing approval could significantly harm our operating results, our ability to raise capital needed to commercialize products and our overall financial condition.

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;
- withdrawal of clinical trial participants;
- delay or termination of our clinical trial;
- 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
- injury to our reputation;
- a decline in our stock price.

Our inability to maintain 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 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.

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Risks Related to Our Dependence on Third Parties

We rely on third parties, such as contract research organizations, or CROs, to conduct 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 collaborators, where applicable, design the clinical trials for our product candidates, but we have relied, and will 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 plan to continue to rely on these third parties to conduct our ongoing any future 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.

We rely on third-party manufacturers to produce our preclinical and clinical product candidate 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 do not possess all of the capabilities to fully commercialize any of our product candidates on our own. 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 product candidates or to 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 product candidates. 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 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, quantity or timeframe 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 matures, we will have a greater need for 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 in the event that one or more of our product candidates gains marketing approval, third parties with whom we currently work will need to increase their scale of production or we will need to secure alternate suppliers.

We may not be successful in establishing or maintaining strategic partnerships to further the development of our therapeutic programs. Additionally, if any of our current or future strategic partners fails to perform its obligations or terminates the partnership, the development and commercialization of the product candidates under such agreement could be delayed or terminated. Such failures could have a material adverse effect on our operations and business.

Our success will depend in significant part on our ability to attract and maintain strategic partners and strategic relationships with major biotechnology or pharmaceutical companies to support the development and commercialization of our product candidates. In these partnerships, we would expect our strategic partner to provide capabilities in research, development, marketing and sales, in addition to funding.

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 product candidates may be deemed to be at too early of a stage of development for collaborative effort or third parties may not view our product candidates as having the requisite potential.

Any delay in entering into new strategic partnership agreements related to our product candidates could have an adverse effect on our business, including delaying the development and commercialization of our product candidates. If we are not able to establish and maintain strategic partnerships:

- we will have fewer resources with which to continue to operate our business;
- the development of certain of our product candidates may be terminated or delayed; and
- our cash expenditures needed to develop such product candidates would increase significantly and we do not have the cash resources to develop our product candidates on our own.

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. Furthermore, we may not be able to maintain such strategic partnerships if, for example, development or approval of a product candidate is delayed, sales of an approved product are disappointing or the partner experiences its own financial or operational constraints or a change in business strategy. 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. For example, Ophthotech Corporation provided us formal written notice in January 2017 that it would not be able to move forward with the development of tivozanib outside of Asia and the Middle East for the potential diagnosis, prevention and treatment of non-oncologic diseases or conditions of the eye in humans pursuant to a research and exclusive option agreement with us and exercised its right to terminate its agreement with us, effective April 2017. Similarly, in June 2016, JSC “Pharmstandard-Ufimskiy Vitamin Plant” notified us that, due to economic and market changes in Russia, it was exercising its right to terminate its license agreement with us to develop and commercialize tivozanib in the territories of Russia, Ukraine and the Commonwealth of Independent States, effective

September 9, 2016. Our current partner Biodesix can opt-out of its agreement with us at any time prior to the first commercial sale of ficlatuzumab, at which point Biodesix would not be responsible for any future costs associated with developing and commercializing ficlatuzumab other than any ongoing clinical studies.

Much of the potential revenue from any of our strategic partnerships will likely consist of contingent payments, such as development milestones and royalties payable on sales of any successfully developed drugs. Any such contingent revenue will depend upon our, and our strategic partners', ability to successfully develop, introduce, market and sell new drugs. In some cases, we are not involved in these processes, and we depend entirely on our strategic partners. Any of our 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.

Risks Related to Our Intellectual Property Rights

We could be unsuccessful in obtaining or maintaining adequate patent protection for one or more of our product candidates, which could result in competition and a decrease in the potential market share for 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 and factual considerations. The standards applied by the United States Patent and Trademark Office, or USPTO, 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 USPTO will grant with respect to the antibodies in our antibody product pipeline is uncertain. It is possible that the USPTO 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, including biosimilar antibodies, thereby decreasing our market share.

If we do not obtain patent term extensions under the Hatch-Waxman Act and similar non-U.S. legislation to extend the term of patents covering each of our product candidates, our business may be materially harmed.

Patents have a limited duration. The term of a U.S. patent, if granted from an application filed on or after June 8, 1995, is generally 20 years from its earliest U.S. non-provisional filing date. Even if patents covering our product candidates are obtained, once the patents expire, we may be open to competition from competitive medications. Given the amount of time required for the development, testing and regulatory review of new product candidates, patents protecting such candidates might expire before or shortly after such candidates are commercialized. As a result, our owned or in-licensed patent rights may not provide us with sufficient rights to exclude others from commercializing products similar or identical to ours.

Depending upon the circumstances, the term of our owned and in-licensed patent rights that cover our product candidates may be extended in the U.S. under the Hatch-Waxman Act and by similar legislation in other countries for delays incurred when seeking marketing approval for a drug candidate. For example, the Hatch-Waxman Act permits a patent term extension of up to five years for a patent covering an approved product as compensation for effective patent term lost during product development and the FDA regulatory review process. However, we may not receive an extension if we fail to apply within the applicable deadline, fail to apply prior to expiration of relevant patents or otherwise fail to satisfy applicable requirements. Moreover, the length of the extension could be less than we request. If we are unable to obtain patent term extension or the term of any such extension is less than we request, the period during which we can enforce our patent rights for that product will be shortened and our competitors may obtain approval to market competing products sooner. As a result, our revenue from applicable products could be reduced, possibly materially.

The U.S. patent rights that we exclusively license covering tivozanib are scheduled to expire from 2018 to 2023. The U.S. patent covering the molecule and its therapeutic use is scheduled to expire in 2022. In view of the length of time tivozanib has been under regulatory review at the FDA, however, a patent term extension of up to 5 years may be available, which, if granted, would

extend the term of this patent until 2027. However, the length of the extension could be less than we request, or no extension may be granted at all. If we are unable to obtain a patent term extension or the term of any such extension is less than we request, the period of time during which we can enforce our patent rights covering tivozanib or its use will be shortened, and our competitors may obtain approval to market a competing product sooner. As a result, our potential revenue from tivozanib could be materially reduced, causing material harm to our business.

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

If we or one of our strategic 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 one or more statutory requirements for patentability, including, for example, lack of novelty, obviousness, lack of written description or non-enablement. In addition, patent validity challenges may, under certain circumstances, be based upon non-statutory obviousness-type double patenting, which, if successful, could result in a finding that the claims are invalid for obviousness-type double patenting or the loss of patent term, including a patent term adjustment granted by the United States Patent and Trademark Office, if a terminal disclaimer is filed to obviate a finding of obviousness-type double patenting. Grounds for an unenforceability assertion could be an allegation that someone connected with prosecution of the patent withheld relevant information from the USPTO, or made a misleading statement, during prosecution. Additionally, third parties are able to challenge the validity of issued patents through administrative proceedings in the patent offices of certain countries, including the USPTO and the European Patent Office. 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. 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 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 a third party United States patent that contains 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 patent owners indicating that they believe we may need a license from them in order to avoid infringing their patent rights. 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. In the event that an owner of one or more of these patents were to bring an infringement action against us, we may have to argue that our product, its manufacture or use does not infringe a valid claim of the patent in question. Furthermore, 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 commercially 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 an 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 our partnerships 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 uncertainties associated with litigation could have a material adverse effect on our ability to raise the funds necessary to continue our clinical trials, 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.

An intellectual property litigation could lead to unfavorable publicity that could harm our reputation and cause 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. In such event, the market price of our common stock may decline.

AV-380 and tivozanib 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 would be harmed and our partnerships could be terminated.

Certain of our product candidates and out-licensing arrangements depend on patents and/or patent applications owned by other companies or institutions with which we have entered into intellectual property licenses. In particular, we hold exclusive licenses from St. Vincent’s for therapeutic applications that benefit from inhibition or decreased

expression or activity of MIC-1, which we refer to as GDF15 and which we used in our AV-380 program, and from KHK for tivozanib. We may 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, a licensor could claim that we have materially breached a license agreement and terminate the license, thereby removing our or our licensees' ability to obtain regulatory approval for and to market any product covered by such license. 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, identical products. In addition, the partners to which we have sublicensed certain rights under these licenses, including Novartis and EUSA, would likely have grounds for terminating our partnerships if these licenses are terminated or the underlying patents are not maintained or enforced. This could have a material adverse effect on our results of operations, our competitive business position and our business prospects.

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 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 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 confidential information, then our ability to obtain patent protection or to protect our trade secret information may be jeopardized.

Intellectual property rights may not address all potential threats to our competitive advantage.

The degree of future protection afforded by our intellectual property rights is uncertain because intellectual property rights have limitations, and may not adequately protect our business, or permit us to maintain our competitive advantage. The following examples are illustrative:

- Others may be able to make compounds that are similar to our product candidates but that are not covered by the claims of the patents that we own or have exclusively licensed.
- We or our licensors or strategic partners might not have been the first to make the inventions covered by the issued patent or pending patent application that we own or have exclusively licensed.
- We or our licensors or strategic partners might not have been the first to file patent applications covering certain of our inventions.
- Others may independently develop similar or alternative technologies or duplicate any of our technologies without infringing our intellectual property rights.
- It is possible that our pending patent applications will not lead to issued patents.
- Issued patents that we own or have exclusively licensed may not provide us with a competitive advantage; for example, our issued patents may not be broad enough to prevent the commercialization of competitive antibodies that are biosimilar to one or more of our antibody products, or may be held invalid or unenforceable, as a result of legal challenges by our competitors.
- Our competitors might conduct research and development activities in countries where we do not have patent rights and then use the information learned from such activities to develop competitive products for sale in our major

commercial markets.

- We may not develop additional proprietary technologies that are patentable.
- The patents of others may have an adverse effect on our business.

Changes in U.S. patent law could diminish the value of patents in general, thereby impairing our ability to protect our products.

As is the case with other biopharmaceutical companies, our success is heavily dependent on intellectual property, particularly patents. Obtaining and enforcing patents in the biopharmaceutical industry involve both technological complexity and legal

complexity. Therefore, obtaining and enforcing biopharmaceutical patents is costly, time-consuming and inherently uncertain. In addition, several recent events have increased uncertainty with regard to our ability to obtain patents in the future and the value of patents once obtained. Among these, in September 2011, patent reform legislation passed by Congress was signed into law in the U.S. The new patent law introduces changes including a first-to-file system for determining which inventors may be entitled to receive patents, and a new post-grant review process that allows third parties to challenge newly issued patents. It remains to be seen how the biopharmaceutical industry will be affected by such changes in the patent system. In addition, the U.S. Supreme Court has ruled on several patent cases in recent years, either narrowing the scope of patent protection available in specified circumstances or weakening the rights of patent owners in specified situations. Depending on decisions by the U.S. Congress, the federal courts, and the USPTO, the laws and regulations governing patents could change in unpredictable ways that could weaken our ability to obtain new patents or to enforce our existing patents and patents that we might obtain in the future.

Risks Related to Regulatory Approval and Marketing of Our Product Candidates and Other Legal Compliance Matters

Even if we complete the necessary preclinical studies and clinical trials, the regulatory approval process is expensive, time-consuming and uncertain and may prevent us from obtaining approvals for the commercialization of some or all of our product candidates. If we or our collaborators are not able to obtain, or if there are delays in obtaining, required regulatory approvals, we will not be able to commercialize our product candidates, and our ability to generate revenue will be materially impaired.

Our product candidates and the activities associated with their development and commercialization, including their design, testing, manufacture, safety, efficacy, recordkeeping, labeling, storage, approval, advertising, promotion, sale and distribution, export and import, are subject to comprehensive regulation by the FDA and other regulatory agencies in the United States and by the EMA and comparable regulatory authorities in other countries. Failure to obtain marketing approval for a product candidate will prevent us from commercializing the product candidate. We and our collaborators have not received approval to market any of our product candidates from regulatory authorities in any jurisdiction. We have only limited experience in filing and supporting the applications necessary to gain marketing approvals and expect to rely on third-party contract research organizations to assist us in this process.

Securing marketing approval requires the submission of extensive preclinical and clinical data and supporting information to the various regulatory authorities for each therapeutic indication to establish the product candidate's safety and efficacy. Securing regulatory approval also requires the submission of information about the product manufacturing process to, and inspection of manufacturing facilities by, the relevant regulatory authority. Our product candidates may not be effective, may be only moderately effective or may prove to have undesirable or unintended side effects, toxicities or other characteristics that may preclude our obtaining marketing approval or prevent or limit commercial use.

The process of obtaining marketing approvals, both in the United States and abroad, is expensive, may take many years if additional clinical trials are required, if approval is obtained at all, and can vary substantially based upon a variety of factors, including the type, complexity and novelty of the product candidates involved. Changes in marketing approval policies during the development period, changes in or the enactment of additional statutes or regulations, or changes in regulatory review for each submitted product application, may cause delays in the approval or rejection of an application. The FDA and comparable authorities in other countries have substantial discretion in the approval process and may refuse to accept any application or may decide that our data is insufficient for approval and require additional preclinical, clinical or other studies. In addition, varying interpretations of the data obtained from preclinical and clinical testing could delay, limit or prevent marketing approval of a product candidate. Any marketing approval we or our collaborators ultimately obtain may be limited or subject to restrictions or post-approval commitments that render the approved product not commercially viable.

Accordingly, if we or our collaborators experience delays in obtaining approval or if we fail to obtain approval of our product candidates, the commercial prospects for our product candidates may be harmed and our ability to generate revenues will be materially impaired.

Failure to obtain marketing approval in foreign jurisdictions would prevent our product candidates from being marketed in such jurisdictions.

In order to market and sell our medicines in the European Union and many other jurisdictions, we or our collaborators must obtain marketing approvals and comply with numerous and varying regulatory requirements. The approval procedure varies among countries and can involve additional testing. The time required to obtain approval may differ substantially from that required to obtain FDA approval. The regulatory approval process outside the United States generally includes all of the risks associated with obtaining FDA approval. In addition, in many countries outside the United States, a product be approved for reimbursement before the product can be approved for sale in that country. We or our collaborators may not obtain approvals from regulatory authorities outside the United States on a timely basis, if at all. Approval by the FDA does not ensure approval by regulatory authorities in other countries or jurisdictions, and approval by one regulatory authority outside the United States does not ensure approval by regulatory authorities in

other countries or jurisdictions or by the FDA. We may not be able to file for marketing approvals and may not receive necessary approvals to commercialize our products in any market.

We may not be able to obtain orphan drug designation or orphan drug exclusivity for our product candidates, and, even if we do, that exclusivity may not prevent the FDA or the EMA from approving other competing products.

Regulatory authorities in some jurisdictions, including the United States and Europe, may designate drugs and biologics for relatively small patient populations as orphan drugs. Under the Orphan Drug Act, the FDA may designate a product as an orphan drug if it is intended to treat a rare disease or condition, which is generally defined as a patient population of fewer than 200,000 individuals annually in the United States. We or our collaborators may seek orphan drug designations for other product candidates and may be unable to obtain such designations.

Even if we obtain orphan drug designation for a product candidate, we may not be able to obtain orphan drug exclusivity for that candidate. Generally, a product with orphan drug designation only becomes entitled to orphan drug exclusivity if it receives the first marketing approval for the indication for which it has such designation, in which case the FDA or the EMA will be precluded from approving another marketing application for the same product for that indication for the applicable exclusivity period. The applicable exclusivity period is seven years in the United States and ten years in Europe. The European exclusivity period can be reduced to six years if a product no longer meets the criteria for orphan drug designation or if the product is sufficiently profitable so that market exclusivity is no longer justified. Orphan drug exclusivity may be lost if the FDA or the EMA determines that the request for designation was materially defective or if the manufacturer is unable to assure sufficient quantity of the product to meet the needs of patients with the rare disease or condition.

Even if we obtain orphan drug exclusivity for a product, that exclusivity may not effectively protect the product from competition because different products can be approved for the same condition. Even after an orphan drug is approved, the FDA can subsequently approve the same drug or biologic for the same condition if the FDA concludes that the later product is clinically superior in that it is shown to be safer, more effective or makes a major contribution to patient care.

Even if we or our collaborators obtain marketing approvals for our product candidates, the terms of approvals and ongoing regulation of our products may limit how we manufacture and market our products, which could materially impair our ability to generate revenue.

Once marketing approval has been granted, an approved product and its manufacturer and marketer are subject to ongoing review and extensive regulation. We and our collaborators must therefore comply with requirements concerning advertising and promotion for any of our product candidates for which we obtain marketing approval. Promotional communications with respect to prescription products are subject to a variety of legal and regulatory restrictions and must be consistent with the information in the product's approved labeling. Thus, we will not be able to promote any products we develop for indications or uses for which they are not approved.

In addition, manufacturers of approved products and those manufacturers' facilities are required to comply with extensive FDA requirements, including ensuring that quality control and manufacturing procedures conform to cGMPs, which include requirements relating to quality control and quality assurance as well as the corresponding maintenance of records and documentation and reporting requirements. We and our collaborators and our contract manufacturers could be subject to periodic unannounced inspections by the FDA to monitor and ensure compliance with cGMPs.

Accordingly, assuming we receive marketing approval for one or more of our product candidates, we will continue to expend time, money and effort in all areas of regulatory compliance, including manufacturing, production, product surveillance and quality control.

If we and our collaborators are not able to comply with post-approval regulatory requirements, we could have the marketing approvals for our products withdrawn by regulatory authorities and our ability to market any products could be limited, which could adversely affect our ability to achieve or sustain profitability. Further, the cost of compliance with post-approval regulations may have a negative effect on our operating results and financial condition.

Any product candidate for which we or our collaborators obtain marketing approval could be subject to restrictions or withdrawal from the market and we may be subject to substantial penalties if we fail to comply with regulatory requirements or if we experience unanticipated problems with our product candidates, when and if any of them are approved.

Any product candidate for which we or our collaborators obtain marketing approval, along with the manufacturing processes, post-approval clinical data, labeling, advertising and promotional activities for such product, will be subject to continual requirements

of and review by the FDA and other regulatory authorities. These requirements include submissions of safety and other post-marketing information and reports, registration and listing requirements, cGMP requirements relating to quality control and manufacturing, quality assurance and corresponding maintenance of records and documents, and requirements regarding the distribution of samples to physicians and recordkeeping. Even if marketing approval of a product candidate is granted, the approval may be subject to limitations on the indicated uses for which the product may be marketed or to the conditions of approval, or contain requirements for costly post-marketing testing and surveillance to monitor the safety or efficacy of the medicine, including the requirement to implement a risk evaluation and mitigation strategy.

The FDA and other agencies, including the Department of Justice, or the DOJ, closely regulate and monitor the post-approval marketing and promotion of products to ensure that they are marketed and distributed only for the approved indications and in accordance with the provisions of the approved labeling. The FDA and DOJ impose stringent restrictions on manufacturers' communications regarding off-label use and if we do not market our products for their approved indications, we may be subject to enforcement action for off-label marketing. Violations of the Federal Food, Drug, and Cosmetic Act and other statutes, including the False Claims Act, relating to the promotion and advertising of prescription products may lead to investigations and enforcement actions alleging violations of federal and state health care fraud and abuse laws, as well as state consumer protection laws.

In addition, later discovery of previously unknown adverse events or other problems with our products, manufacturers or manufacturing processes, or failure to comply with regulatory requirements, may yield various results, including:

- restrictions on such products, manufacturers or manufacturing processes;
- restrictions on the labeling or marketing of a product;
- restrictions on distribution or use of a product;
- requirements to conduct post-marketing studies or clinical trials;
- warning letters or untitled letters;
- withdrawal of the products from the market;
- refusal to approve pending applications or supplements to approved applications that we submit;
- recall of products;
- damage to relationships with collaborators;
- unfavorable press coverage and damage to our reputation;
- fines, restitution or disgorgement of profits or revenues;
- suspension or withdrawal of marketing approvals;
- refusal to permit the import or export of our products;
- product seizure;
- injunctions or the imposition of civil or criminal penalties; and
- litigation involving patients using our products.

Non-compliance with European Union requirements regarding safety monitoring or pharmacovigilance, and with requirements related to the development of products for the pediatric population, can also result in significant financial penalties. Similarly, failure to comply with the European Union's requirements regarding the protection of personal information can also lead to significant penalties and sanctions.

Our relationships with healthcare providers, physicians and third party payors will be subject to applicable anti-kickback, fraud and abuse and other healthcare laws and regulations, which, in the event of a violation, could expose us to criminal sanctions, civil penalties, contractual damages, reputational harm and diminished profits and future earnings.

Healthcare providers, physicians and third party payors will play a primary role in the recommendation and prescription of any product candidates for which we obtain marketing approval. Our future arrangements with healthcare providers, physicians and third party payors may expose us to broadly applicable fraud and abuse and other healthcare laws and regulations that may constrain the business or financial arrangements and relationships through which we market, sell and distribute any products for which we obtain marketing approval. Restrictions under applicable federal and state healthcare laws and regulations include the following:

- the federal Anti-Kickback Statute prohibits, among other things, persons from knowingly and willfully soliciting, offering, receiving or providing remuneration, directly or indirectly, in cash or in kind, to induce or reward, or in return for, either the referral of an individual for, or the purchase, order or recommendation or arranging of, any good or service, for which payment may be made under a federal healthcare program such as Medicare and Medicaid;
- the federal False Claims Act imposes criminal and civil penalties, including through civil whistleblower or qui tam actions, against individuals or entities for, among other things, knowingly presenting, or causing to be presented, false or fraudulent claims for payment by a federal healthcare program or making a false statement or record material to payment of a false claim or avoiding, decreasing or concealing an obligation to pay money to the federal government, with potential liability including mandatory treble damages and significant per-claim penalties, currently set at $10,781 to $21,563 per false claim;
- the federal Health Insurance Portability and Accountability Act of 1996, or HIPAA, imposes criminal and civil liability for executing a scheme to defraud any healthcare benefit program or making false statements relating to healthcare matters;
- HIPAA, as amended by the Health Information Technology for Economic and Clinical Health Act and its implementing regulations, also imposes obligations, including mandatory contractual terms, with respect to safeguarding the privacy, security and transmission of individually identifiable health information;
- the federal Physician Payments Sunshine Act requires applicable manufacturers of covered products to annually report to CMS (i) payments and other transfers of value to physicians and teaching hospitals, and (ii) certain physician ownership or investment interests; and
- analogous state and foreign laws and regulations, such as state anti-kickback and false claims laws and transparency statutes, may apply to sales or marketing arrangements and claims involving healthcare items or services reimbursed by third party payors, including private insurers.

Some state laws require pharmaceutical companies to comply with the pharmaceutical industry’s voluntary compliance guidelines and the relevant compliance guidance promulgated by the federal government and may require manufacturers to report information related to payments and other transfers of value to other healthcare providers and healthcare entities, or marketing expenditures. State and foreign laws also govern the privacy and security of health information in some circumstances, many of which differ from each other in significant ways and often are not preempted by HIPAA, thus complicating compliance efforts.

If our operations are found to be in violation of any of the laws described above or any governmental regulations that apply to us, we may be subject to penalties, including civil and criminal penalties, damages, fines, individual imprisonment, integrity obligations, exclusion from funded healthcare programs and the curtailment or restructuring of our operations. Any such penalties could adversely affect our financial results. We are developing and implementing a corporate compliance program designed to ensure that we will market and sell any future products that we successfully develop from our product candidates in compliance with all applicable laws and regulations, but we cannot guarantee that this program will protect 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.

Efforts to ensure that our business arrangements with third parties will comply with applicable healthcare laws and regulations will involve substantial costs. It is possible that governmental authorities will conclude that our business practices may not comply with current or future statutes, regulations or case law involving applicable fraud and abuse or other healthcare laws and regulations. If our operations are found to be in violation of any of these laws or any other governmental regulations that may apply to us, we may be subject to significant civil, criminal and administrative penalties, damages, fines, individual imprisonment, integrity obligations, exclusion from government funded healthcare programs, such as Medicare and Medicaid, and the curtailment or restructuring of our operations. If any of the physicians or other healthcare providers or entities with whom we expect to do business is found to be not in compliance with applicable laws, they may be subject to criminal, civil or administrative sanctions, including exclusion from government funded healthcare programs.

Current and future legislation may increase the difficulty and cost for us or our collaborators to obtain marketing approval of our product candidates and affect the prices we may obtain.

In the United States and some foreign jurisdictions, there have been a number of legislative and regulatory changes and proposed changes regarding the healthcare system that could, among other things, prevent or delay marketing approval of our product candidates, restrict or regulate post-approval activities and affect our ability to profitably sell any products for which we obtain marketing approval. We expect that current laws, as well as other healthcare reform measures that may be adopted in the future, may result in more rigorous coverage criteria and in additional downward pressure on the price that we may receive for any approved products.

For example, in March 2010, President Obama signed into law the Affordable Care Act, as amended by the Health Care and Education Affordability Reconciliation Act, or collectively the ACA. In January 2017, Congress voted to adopt a budget resolution for fiscal year 2017, or the Budget Resolution, that authorizes the implementation of legislation that would repeal portions of the ACA. The Budget Resolution is not a law, however, it is widely viewed as the first step toward the passage of legislation that would repeal certain aspects of the ACA. Further, on January 20, 2017, President Trump signed an Executive Order directing federal agencies with authorities and responsibilities under the ACA to waive, defer, grant exemptions from, or delay the implementation of any provision of the ACA that would impose a fiscal or regulatory burden on states, individuals, healthcare providers, health insurers, or manufacturers of pharmaceuticals or medical devices. Congress also could consider subsequent legislation to replace elements of the ACA that are repealed.

Other legislative changes have been proposed and adopted since the ACA was enacted. These changes include the Budget Control Act of 2011, which, among other things, led to aggregate reductions to Medicare payments to providers of up to 2% per fiscal year that started in 2013 and, due to subsequent legislation, will continue until 2025. In addition, the American Taxpayer Relief Act of 2012, among other things, reduced Medicare payments to several providers and increased the statute of limitations period for the government to recover overpayments to providers from three to five years. These new laws may result in additional reductions in Medicare and other healthcare funding and otherwise affect the prices we may obtain for any of our product candidates for which regulatory approval is obtained.

We expect that other healthcare reform measures that may be adopted in the future, may result in additional reductions in Medicare and other healthcare funding, more rigorous coverage criteria, new payment methodologies and in additional downward pressure on the price that we receive for any approved product. Any reduction in reimbursement from Medicare or other government programs may result in a similar reduction in payments from private payors. The implementation of cost containment measures or other healthcare reforms may prevent us from being able to generate revenue, attain profitability, or commercialize our products.

In addition, with the new Administration and Congress, there will likely be additional legislative changes, including repeal and replacement of certain provisions of the ACA. It remains to be seen, however, precisely what the new legislation will provide, when it will be enacted and what impact it will have on the availability of healthcare and containing or lowering the cost of healthcare. Such reforms could have an adverse effect on anticipated revenue from product candidates that we may successfully develop and for which we may obtain marketing approval and may affect our overall financial condition and ability to develop product candidates.

Moreover, legislative and regulatory proposals have been made to expand post-approval requirements and restrict sales and promotional activities for pharmaceutical products. We cannot be sure whether additional legislative changes will be enacted, or whether the FDA regulations, guidance or interpretations will be changed, or what the impact of such changes on the marketing approvals of our product candidates, if any, may be. In addition, increased scrutiny by the United States Congress of the FDA’s approval process may significantly delay or prevent marketing approval, as well as subject us and any collaborators to more stringent product labeling and post-marketing testing and other requirements.

Laws and regulations governing any international operations we may have in the future may preclude us from developing, manufacturing and selling certain products outside of the United States and require us to develop and implement costly compliance programs.

If we expand our operations outside of the United States, we must dedicate additional resources to comply with numerous laws and regulations in each jurisdiction in which we plan to operate. The Foreign Corrupt Practices Act, or FCPA, prohibits any U.S. individual or business from paying, offering, authorizing payment or offering of anything of value, directly or indirectly, to any foreign official, political party or candidate for the purpose of influencing any act or decision of the foreign entity in order to assist the individual or business in obtaining or retaining business. The FCPA also obligates companies whose securities are listed in the United States to comply with certain accounting provisions requiring the company to maintain books and records that accurately and fairly reflect all transactions of the corporation, including international subsidiaries, and to devise and maintain an adequate system of internal accounting controls for international operations.

Compliance with the FCPA is expensive and difficult, particularly in countries in which corruption is a recognized problem. In addition, the FCPA presents particular challenges in the pharmaceutical industry, because, in many countries, hospitals are operated by the government, and doctors and other hospital employees are considered foreign officials. Certain payments to hospitals in connection with clinical trials and other work have been deemed to be improper payments to government officials and have led to FCPA enforcement actions.

Various laws, regulations and executive orders also restrict the use and dissemination outside of the United States, or the sharing with certain non-U.S. nationals, of information classified for national security purposes, as well as certain products and technical data relating to those products. If we expand our presence outside of the United States, it will require us to dedicate additional resources to comply with these laws, and these laws may preclude us from developing, manufacturing, or selling certain products and product candidates outside of the United States, which could limit our growth potential and increase our development costs.

The failure to comply with laws governing international business practices may result in substantial civil and criminal penalties and suspension or debarment from government contracting. The Securities and Exchange Commission, or SEC, also may suspend or bar issuers from trading securities on U.S. exchanges for violations of the FCPA's accounting provisions.

If we fail to comply with environmental, health and safety laws and regulations, we could become subject to fines or penalties or incur costs that could have a material adverse effect on our business.

We are subject to numerous environmental, health and safety laws and regulations, including those governing laboratory procedures and the handling, use, storage, treatment and disposal of hazardous materials and wastes. From time to time and in the future, our operations may involve the use of hazardous and flammable materials, including chemicals and biological materials, and may also produce hazardous waste products. Even if we contract with third parties for the disposal of these materials and waste products, we cannot completely eliminate the risk of contamination or injury resulting from these materials. In the event of contamination or injury resulting from the use or disposal of our hazardous materials, we could be held liable for any resulting damages, and any liability could exceed our resources. We also could incur significant costs associated with civil or criminal fines and penalties for failure to comply with such laws and regulations.

We maintain workers' compensation insurance to cover us for costs and expenses we may incur due to injuries to our employees resulting from the use of hazardous materials, but this insurance may not provide adequate coverage against potential liabilities. However, we do not maintain insurance for environmental liability or toxic tort claims that may be asserted against us.

In addition, we may incur substantial costs in order to comply with current or future environmental, health and safety laws and regulations. Current or future environmental laws and regulations may impair our research, development or production efforts, which could adversely affect our business, financial condition, results of operations or prospects. In addition, failure to comply with these laws and regulations may result in substantial fines, penalties or other sanctions.

Governments outside the United States tend to impose strict price controls, which may adversely affect our revenues, if any.

In some countries, such as the countries of the European Union, the pricing of prescription pharmaceuticals is subject to governmental control and access. In these countries, pricing negotiations with governmental authorities can take considerable time after the receipt of marketing approval for a product. To obtain reimbursement or pricing approval in some countries, we or our collaborators may be required to conduct a clinical trial that compares the cost-effectiveness of our product to other available therapies. If reimbursement of our products is unavailable or limited in scope or amount, or if pricing is set at unsatisfactory levels, our business could be materially harmed.

We rely significantly upon information technology and any failure, inadequacy, interruption or security lapse of that technology, including any cyber security incidents, could harm our ability to operate our business effectively.

Despite the implementation of security measures, our internal computer systems and those of third parties with which we contract are vulnerable to damage from cyber-attacks, computer viruses, unauthorized access, natural disasters, terrorism, war and telecommunication and electrical failures. System failures, accidents or security breaches could cause interruptions in our operations, and could result in a material disruption of our clinical and commercialization activities and business operations, in addition to possibly requiring substantial expenditures of resources to remedy. The loss of clinical trial data could result in delays in our regulatory approval efforts and significantly increase our costs to recover or reproduce the data. To the extent that any disruption or security breach were to result in a loss of, or damage to, our data or applications, or inappropriate public disclosure of confidential or proprietary information, we could incur liability and our product development and commercialization efforts could be delayed.

Risks Related to Employee Matters and Managing Growth

If we fail to attract and keep senior management, 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 personnel. We are highly dependent upon our senior management, as well as others on our management team. We have completed several reductions in force related to restructurings we have completed in the past, which could make it more difficult to retain or attract employees in the future. The loss of services of employees, and in particular, of a member of management could delay or prevent our ability to successfully maintain or enter into new licensing arrangements or collaborations, the successful development of our product candidates, 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 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.

Risks Related to Ownership of Our Common Stock

If we fail to meet the requirements for continued listing on the Nasdaq Global Select Market, our common stock could be delisted from trading, which would decrease the liquidity of our common stock and our ability to raise additional capital.

Our common stock is currently listed for quotation on the Nasdaq Global Select Market. We are required to meet specified requirements to maintain our listing on the Nasdaq Global Select Market, including, among other things, a minimum bid price of $1.00 per share. On October 11, 2016, we received a deficiency letter from the Listing Qualifications Department, or the Staff, of the Nasdaq Stock Market notifying us that, for the last 30 consecutive business days, the bid price for our common stock had closed below the minimum $1.00 per share requirement for continued inclusion on the Nasdaq Global Select Market. We have been provided an initial period of 180 calendar days, or until April 10, 2017, to regain compliance with the minimum bid price requirement. If, at any time before April 10, 2017, the bid price for our common stock closes at $1.00 or more for a minimum of 10 consecutive trading days, we may be eligible to regain compliance with the minimum bid price requirement. Under certain circumstances, Nasdaq could require that the bid price exceed $1.00 for more than ten consecutive trading days before determining that we comply with Nasdaq’s continued listing standards. From October 11, 2016, the date of the deficiency letter, to the date of filing of this Annual Report on Form 10-K, our common stock had not closed above $1.00 on any trading day.

To maintain our common stock listing on the Nasdaq Global Select Market, we are also required to maintain a minimum market value of listed securities, or MVLS, of $50,000,000. On January 6, 2017, we received a deficiency letter from the Staff notifying us that, for the prior 30 consecutive trading days, our MVLS had fallen below the minimum $50,000,000 requirement for continued inclusion on the Nasdaq Global Select Market. On March 1, 2017, we received a follow-up letter from the Staff notifying us that, as of February 28, 2017, we had regained compliance with the minimum MVLS requirement because our MVLS was above $50,000,000 for 10 consecutive trading days. Although we regained compliance with the MVLS requirement as of February 28, 2017, our MVLS is still low and we may fail to meet the MVLS requirement again in the future.

If we fail to satisfy the Nasdaq Global Select Market's continued listing requirements, we may transfer to the Nasdaq Capital Market, which generally has lower financial requirements for initial listing, to avoid delisting, or, if we fail to meet its listing requirements, the OTC Bulletin Board. However, we may not be able to satisfy the initial listing requirements for the Nasdaq Capital Market. For example, we do not currently meet the Nasdaq Capital Market's stockholders' equity requirement. A transfer of our listing to the Nasdaq Capital Market or having our common stock trade on the OTC Bulletin Board could adversely affect the liquidity of our common stock. Any such event could make it more difficult to dispose of, or obtain accurate quotations for the price of, our common stock, and there also would likely be a reduction in our coverage by securities analysts and the news media, which could cause the price of our common stock to decline further. We may also face other material adverse consequences in such event, such as negative publicity, a decreased ability to obtain additional financing, diminished investor and/or employee confidence, and the loss of business development opportunities, some or all of which may contribute to a further decline in our stock price.

The market price of our common stock has been, and is likely to be, highly volatile, and could fall below the price you paid. A significant decline in the value of our stock price could also result in securities class-action litigation against us.

The market price of our common stock has been, and is likely to continue to be, highly volatile and subject to wide fluctuations in price in response to various factors, many of which are beyond our control, including:

- new products, product candidates or new uses for existing products introduced or announced by our strategic partners, or our competitors, and the timing of these introductions or announcements;
- actual or anticipated results from and any delays in our clinical trials;
- results of regulatory reviews relating to our product candidates;
- the results of our efforts to develop, acquire or in-license additional product candidates or products;
- disputes or other developments relating to proprietary rights, including patents, litigation matters and our ability to obtain patent protection for our technologies;
- announcements by us of material developments in our business, financial condition and/or operations;
- announcements by us or our competitors of significant acquisitions, strategic partnerships, joint ventures and capital commitments;
- additions or departures of key scientific or management personnel;
- conditions or trends in the biotechnology and biopharmaceutical industries;
- actual or anticipated changes in earnings estimates, development timelines or recommendations by securities analysts;
- general economic and market conditions and other factors that may be unrelated to our operating performance or the operating performance of our competitors, including changes in market valuations of similar companies; and
- sales of common stock by us or our stockholders in the future, as well as the overall trading volume of our common stock.

In addition, the stock market in general and the market for biotechnology and biopharmaceutical companies in particular have experienced extreme price and volume fluctuations that have often been unrelated or disproportionate to the operating performance of those companies. These broad market and industry factors may seriously harm the market price of our common stock, regardless of our operating performance.

Periods of volatility in the market for a company's stock are often followed by litigation against the company. For example, since our May 2, 2013 announcement regarding the vote of the Oncologic Drugs Advisory Committee of the FDA, we and certain of our former officers and directors have been involved in a number of legal proceedings, including those described in Part I, Item 3 of this report under the heading "Legal Proceedings". These proceedings and other similar litigation, if instituted against us, could result in substantial costs and diversion of management's attention and resources, which could materially and adversely affect our business and financial condition.

We and our collaborators may not achieve 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 statements we have made about the initiation and completion of clinical trials, filing and approval of regulatory applications and other developments and milestones under our research and development programs and those of our partners and collaborators for tivozanib, ficlatuzumab, AV-203, AV-380 and the AV-353 platform. The actual timing of these events can vary significantly due to a number of factors, including, without limitation, delays or failures in our preclinical studies or clinical trials, the amount of time, effort and resources committed to our programs and the uncertainties inherent in the regulatory approval process. As a result, there can be no assurance that our preclinical studies and clinical trials will advance or be completed in the time frames we expect or announce, that we will make regulatory submissions or receive regulatory approvals as planned or that we will be able to adhere to our current schedule for the achievement of key milestones under any of our programs. If we 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.

Our management has broad discretion over our use of available cash and cash equivalents and might not spend our available cash and cash equivalents in ways that increase the value of your investment.

Our management has broad discretion on where and how to use our cash and cash equivalents and you will be relying on the judgment of our management regarding the application of our available cash and cash equivalents to fund our operations. Our management might not apply our cash and cash equivalents in ways that increase the value of your investment. We expect to use a substantial portion of our cash to fund existing and future research and development of our preclinical and clinical product candidates, with the balance, if any, to be used for working capital and other general corporate purposes, which may in the future include investments in, or acquisitions of, complementary businesses, joint ventures, partnerships, services or technologies. Our management might not be able to yield a significant return, if any, on any investment of this cash. You will not have the opportunity to influence our decisions on how to use our cash reserves.

Fluctuations in our quarterly operating results could adversely affect the price of our common stock.

Our quarterly operating results may fluctuate significantly. Some of the factors that may cause our operating results to fluctuate on a period-to-period basis include:

- the status of our clinical development programs;
- the level of expenses incurred in connection with our clinical development programs, including development and manufacturing costs relating to our clinical development candidates;
- the implementation of restructuring and cost-savings strategies;
- the implementation or termination of collaboration, licensing, manufacturing or other material agreements with third parties, and non-recurring revenue or expenses under any such agreement;
- costs associated with lawsuits against us or other litigation in which we may become involved, including the current purported class action described elsewhere in Part I, Item 3 of this report under the heading “Legal Proceedings”;
- changes in our loan agreement with Hercules, including the existence of any event of default that may accelerate payments due thereunder; and
- compliance with regulatory requirements.

Period-to-period comparisons of our historical and future financial results may not be meaningful, and investors should not rely on them as an indication of future performance. Our fluctuating results may fail to meet the expectations of securities analysts or investors. Our failure to meet these expectations may cause the price of our common stock to decline.

Unstable market and economic conditions may have serious adverse consequences on our business, financial condition and stock price.

As widely reported, global credit and financial markets have been experiencing extreme volatility, and in some cases, disruptions, over the past several years, in many cases, over extended periods. Although certain of these trends have recently showed signs of reversing, there can be no assurance that rapid or extended periods of deterioration in credit and financial markets and confidence in economic conditions will not occur. Our general business strategy may be adversely affected by external economic conditions and a volatile business environment or unpredictable and unstable market conditions. If the equity and credit markets are not favorable at any time we seek to raise capital, it may make any necessary debt or equity financing more difficult, more costly, and more dilutive. Failure to secure any necessary financing in a timely manner and on favorable terms could have a material adverse

effect on our growth strategy, financial performance and stock price and could require us to delay or abandon clinical development plans. In addition, there is a risk that one or more of our current service providers, manufacturers or other partners may not survive economically turbulent times, which could directly affect our ability to attain our operating goals on schedule and on budget.

At December 31, 2016, we had approximately $23.3 million of cash, cash equivalents and marketable securities consisting of cash on deposit with banks, a U. S. government money market fund, and corporate debt securities, including commercial paper. As of the date of this report, we are not aware of any downgrades, material losses, or other significant deterioration in the fair value of our cash equivalents. However, no assurance can be given that deterioration in conditions of the global credit and financial markets would not negatively impact our current portfolio of cash equivalents or our ability to meet our financing objectives. Dislocations in the credit market may adversely impact the value and/or liquidity of cash equivalents owned by us.

There is a possibility that our stock price may decline because of volatility of the stock market and general economic conditions.

Future sales of shares of our common stock, including shares issued upon the exercise of currently outstanding options, could negatively affect our stock price.

A substantial portion of our outstanding common stock can be traded without restriction at any time. Some of these shares are currently restricted as a result of securities laws, but will be able to be sold, subject to any applicable volume limitations under federal securities laws with respect to affiliate sales, in the near future. As such, sales of a substantial number of shares of our common stock in the public market could occur at any time. These sales, or the perception in the market that the holders of a large number of shares intend to sell such shares, could reduce the market price of our common stock. In addition, we have a significant number of shares that are subject to outstanding options. The exercise of these options and the subsequent sale of the underlying common stock could cause a further decline in our stock price. These sales also might make it difficult for us to sell equity securities in the future at a time and at a price that we deem appropriate.

If securities or industry analysts do not publish research or publish inaccurate or unfavorable research about our business, our share price and trading volume could decline.

The trading market for our common stock may depend in part on the research and reports that securities or industry analysts publish about us or our business. We do not have any control over these analysts. There can be no assurance that analysts will cover us, or provide favorable coverage. A lack of research coverage may negatively impact the market price of our common stock. To the event we do have analyst coverage, if one or more analysts downgrade our stock or change their opinion of our stock, our share price would likely decline. In addition, if one or more analysts cease coverage of our company or fail to regularly publish reports on us, we could lose visibility in the financial markets, which could cause our share price or trading volume to decline.

A decline in our stock price may affect future fundraising efforts.

We currently have no product revenues, and depend entirely on funds raised through other sources. One source of such funding is future debt and/or equity offerings. Our ability to raise funds in this manner depends upon, among other things, our stock price, which may be affected by capital market forces, evaluation of our stock by securities analysts, product development success (or failure), and internal management operations and controls.

Provisions in our certificate of incorporation, our by-laws or Delaware law might discourage, delay or prevent a change in control of our company or changes in our management and, therefore, depress the market price of our common stock.

Provisions of our certificate of incorporation, our by-laws or Delaware law may have the effect of deterring unsolicited takeovers or delaying or preventing a change in control of our company or changes in our management, including transactions in which our stockholders might otherwise receive a premium for their shares over then current market prices. In addition, these provisions may limit the ability of stockholders to approve transactions that they may deem to be in their best interest. These provisions include:

- advance notice requirements for stockholder proposals and nominations;
- the inability of stockholders to act by written consent or to call special meetings;
- the ability of our board of directors to make, alter or repeal our by-laws; and
- the ability of our board of directors to designate the terms of and issue new series of preferred stock without stockholder approval, which could be used to institute a rights plan, or a poison pill, that would work to dilute the stock ownership of a potential hostile acquirer, likely preventing acquisitions that have not been approved by our board of directors.

In addition, Section 203 of the Delaware General Corporation Law prohibits a publicly-held Delaware corporation from engaging in a business combination with an interested stockholder, generally a person which together with its affiliates owns, or within the last three years has owned, 15% of our voting stock, for a period of three years after the date of the transaction in which the person became an interested stockholder, unless the business combination is approved in a prescribed manner.

The existence of the foregoing provisions and anti-takeover measures could limit the price that investors might be willing to pay in the future for shares of our common stock. They could also deter potential acquirers of our company, thereby reducing the likelihood that a stockholder could receive a premium for shares of our common stock held by a stockholder in an acquisition.

Our business could be negatively affected as a result of the actions of activist shareholders.

Proxy contests have been waged against companies in the biopharmaceutical industry over the last few years. If faced with a proxy contest, we may not be able to successfully respond to the contest, which would be disruptive to our business. Even if we are successful, our business could be adversely affected by a proxy contest because:

- responding to proxy contests and other actions by activist shareholders may be costly and time-consuming, and may disrupt our operations and divert the attention of management and our employees;
- perceived uncertainties as to the potential outcome of any proxy contest may result in our inability to consummate potential acquisitions, collaborations or in-licensing opportunities and may make it more difficult to attract and retain qualified personnel and business partners; and
- if individuals that have a specific agenda different from that of our management or other members of our board of directors are elected to our board as a result of any proxy contest, such an election may adversely affect our ability to effectively and timely implement our strategic plan and create additional value for our stockholders.

Failure to maintain effective internal controls in accordance with Section 404 of the Sarbanes-Oxley Act could have a material adverse effect on our ability to produce accurate financial statements and on our stock price.

Section 404 of the Sarbanes-Oxley Act of 2002 requires us, on an annual basis, to review and evaluate our internal controls, and requires our independent registered public accounting firm to attest to the effectiveness of our internal controls. Despite our efforts, we can provide no assurance as to our, or our independent registered public accounting firm's, conclusions with respect to the effectiveness of our internal control over financial reporting under Section 404. There is a risk that neither we nor our independent registered public accounting firm will be able to conclude within the prescribed timeframe that our internal control over financial reporting is effective as required by Section 404. This could result in an adverse reaction in the financial markets due to a loss of confidence in the reliability of our financial statements.

In connection with the audit of our consolidated financial statements for the year ended December 31, 2016, we and our independent registered public accounting firm identified a material weakness in our internal control over financial reporting. A material weakness is a deficiency, or a combination of deficiencies, in internal control over financial reporting, such that there is a reasonable possibility that a material misstatement of our annual or interim financial statements will not be prevented or detected on a timely basis. This material weakness related to the failure during 2016 to regularly reconcile the U.K. bank account held by our U.K. subsidiary, Aveo Pharma Limited, that was established to support prior European operations that existed in 2012 to 2013 and had not yet been repatriated. As a result, our internal controls did not detect on a timely basis that, in October 2016, the bank closed this account due to inactivity. At our request, the bank has subsequently remitted the funds to our bank account in the U.S. The account balance at the time the account was closed represented approximately 3% of our total cash, cash equivalents and marketable securities as of December 31, 2016. Although no misappropriation of funds occurred, the control deficiency created the possibility that a misappropriation of funds and/or a material misstatement to our consolidated financial statements may not have been prevented or detected on a timely basis. Accordingly, this control deficiency was considered to represent a material weakness and, as a result, we concluded that our internal control over financial

reporting was not effective as of December 31, 2016.

With respect to this material weakness, certain remediation efforts have been deemed to have occurred as the account has been closed and the funds have been remitted to our bank account in the U.S. However, we continue to evaluate additional controls and procedures that we may design and put in place to address the material weakness. For more information, refer to Part II, Item 9A of this report under the heading “Controls and Procedures—Internal Control Over Financial Reporting.”

We cannot assure you that the measures we have taken to date, together with any measures we may take in the future, will be sufficient to remediate the control deficiency that led to the material weakness in our internal control over financial reporting or to avoid potential future material weaknesses. If we are unable to successfully remediate any material weaknesses in our internal control, or if we identify any additional material weaknesses, the accuracy and timing of our financial reporting may be adversely affected, we may be unable to maintain compliance with securities law requirements regarding timely filing of periodic reports in addition to

applicable stock exchange listing requirements, investors may lose confidence in our financial reporting, and our stock price may decline as a result. We also could become subject to investigations by NASDAQ, the Securities and Exchange Commission, or SEC, or other regulatory authorities.

We do not expect to pay any cash dividends for the foreseeable future.

You should not rely on an investment in our common stock to provide dividend income. We do not anticipate that we will pay any cash dividends to holders of our common stock in the foreseeable future. Instead, we plan to retain any earnings to maintain and expand our existing operations. In addition, our ability to pay cash dividends is currently prohibited by the terms of our debt financing arrangements and any future debt financing arrangement may contain terms prohibiting or limiting the amount of dividends that may be declared or paid on our common stock. Accordingly, investors must rely on sales of their common stock after price appreciation, which may never occur, as the only way to realize any return on their investment. As a result, investors seeking cash dividends should not purchase our common stock.

We might not be able to utilize a significant portion of our net operating loss carryforwards and research and development tax credit carryforwards.

As of December 31, 2016, we had federal and state net operating loss carryforwards of $476.2 million and $366.9 million, respectively, and federal and state research and development tax credit carryforwards of $10.3 million and $4.2 million, respectively, each of which if not utilized will expire at various dates through 2036. These net operating loss and tax credit carryforwards could expire unused and be unavailable to offset future income tax liabilities. In addition, under Section 382 of the Internal Revenue Code of 1986, as amended, and corresponding provisions of state law, if a corporation undergoes an “ownership change,” which is generally defined as a greater than 50% change, by value, in its equity ownership over a three year period, the corporation’s ability to use its pre change net operating loss carryforwards and other pre change tax attributes to offset its post change income may be limited. We may experience ownership changes in the future as a result of subsequent shifts in our stock ownership, some of which may be outside of our control. We have not conducted a detailed study to document whether our historical activities qualify to support the research and development credit carryforwards. A detailed study could result in adjustment to our research and development credit carryforwards. If we determine that an ownership change has occurred and our ability to use our historical net operating loss and tax credit carryforwards is materially limited, or if our research and development carryforwards are adjusted, it would harm our future operating results by effectively increasing our future tax obligations.

ITEM 1B. Unresolved Staff Comments

None.

ITEM 2. Properties

We sublease our principal facilities, which consist of approximately 5,000 square feet of office space located at 1 Broadway, Cambridge, Massachusetts. Our lease arrangement is cancellable with 30 days’ notice to our landlord. We believe that our existing facilities are sufficient for our current needs and for the foreseeable future.

ITEM 3. Legal Proceedings

Two class action lawsuits have been filed against us and certain of our former officers and directors, (Tuan Ha-Ngoc, David N. Johnston, William Slichenmyer and Ronald DePinho), in the United States District Court for the District of Massachusetts, one captioned Paul Sanders v. Aveo Pharmaceuticals, Inc., et al., No. 1:13-cv-11157-JLT, filed on May 9, 2013, and the other captioned Christine Krause v. AVEO Pharmaceuticals, Inc., et al., No. 1:13-cv-11320-JLT, filed on May 31, 2013. On December 4, 2013, the District Court consolidated the complaints as In re AVEO Pharmaceuticals, Inc. Securities Litigation et al., No. 1:13-cv-11157-DJC, and an amended complaint

was filed on February 3, 2014. The amended complaint purported to be brought on behalf of shareholders who purchased our common stock between January 3, 2012 and May 1, 2013. This consolidated amended complaint was dismissed without prejudice on March 20, 2015, and the lead plaintiffs then filed a second amended complaint bringing similar allegations, and which no longer named Mr. DePinho as a defendant. We moved to dismiss again, and after a second round of briefing and oral argument, the court ruled in our favor and dismissed the second amended complaint with prejudice on November 18, 2015. The lead plaintiffs have appealed the court's decision to the United States Court of Appeals for the First Circuit. They also filed a motion to vacate and reconsider the district court's judgment, which we have opposed. On January 3, 2017, the Court granted Plaintiffs' motion to vacate the dismissal and judgment and Plaintiffs filed a motion to dismiss their appeal on February 8, 2017. On February 2, 2017, Plaintiffs filed a third amended complaint, on behalf of shareholders who purchased common stock between May 16, 2012 and May 1, 2013, alleging claims similar to those alleged in the prior complaints, namely that we and certain of our 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 clinical trial in an effort to lead investors to believe that the drug would receive approval from the FDA. On March 2, 2017, we filed an answer to the third amended complaint, and the parties have initiated discovery. The lawsuit seeks unspecified damages, interest, attorneys' fees, and other costs. We deny any allegations of wrongdoing and intend to continue to vigorously defend against this lawsuit. However, there is no assurance that we will be successful in our defense or that insurance will be available or adequate to fund any settlement or judgment or the litigation costs of the action. Moreover, we are unable to predict the outcome or reasonably estimate a range of possible loss at this time.

On April 4, 2014, Karen J. van Ingen, a purported purchaser of AVEO stock, filed a derivative complaint allegedly on behalf of AVEO in the United States District Court for the District of Massachusetts, or the Court, Civil Action No. 1:14-cv-11672-DJC, naming AVEO, as a nominal defendant and also naming as defendants present and former members of our board of directors, including Tuan Ha-Ngoc, Henri A. Termeer, Kenneth M. Bate, Anthony B. Evnin, Robert Epstein, Raju Kucherlapati, Robert C. Young, and Kenneth E. Weg. The complaint alleged 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 lawsuit 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 filed a motion to dismiss the derivative complaint, and after briefing and oral argument, on March 18, 2015 the Court ruled in our favor and dismissed the case with prejudice. The plaintiff then filed a motion seeking to vacate the Court's order of dismissal and permit filing of an amended complaint, which we opposed, and which the Court denied on June 30, 2015. The plaintiff has appealed the Court's decision to the United States Court of Appeals for the First Circuit. The parties have reached an agreement in principle to settle this matter. The settlement involves certain corporate governance changes and other non-monetary relief. The plaintiff is seeking an award of attorney's fees, costs, and expenses in the amount of $822,116, as well as an incentive award of $2,500, both of which we expect will be paid by insurance in the amount ordered by the Court. On September 16, 2016, the Court granted preliminary approval to the proposed settlement. On December 19, 2016, the Court held a final settlement hearing on the terms of the proposed settlement and to consider the award of fees to the plaintiff's attorneys. No objections to the settlement were filed with the Court or raised at the hearing. At the hearing, the Court indicated orally that the settlement will be approved, and heard argument regarding the size of plaintiff's potential attorney's fee award. A formal approval order has not yet entered and the Court has not ruled on the final amount of fees for the plaintiff's attorneys (which, as stated above, are expected to be paid by insurance). Until a formal approval order has been entered, there can be no complete assurance that the Court will approve the settlement.

On July 3, 2013, the staff, or SEC Staff, of the United States Securities and Exchange Commission, or the Commission, served a subpoena on us for documents and information concerning tivozanib, including related communications with the FDA, investors and others. In September 2015, the SEC Staff invited us to discuss the settlement of potential claims asserting that we violated federal securities laws by omitting to disclose to investors the recommendation by the staff of the FDA on May 11, 2012, that we conduct an additional clinical trial with respect to tivozanib. On March 29, 2016, the Commission filed a complaint against us and three of our former officers in the U.S. District Court for the District of Massachusetts alleging that we misled investors about our efforts to obtain FDA approval for tivozanib. Without admitting or denying the allegations in the Commission's complaint, we consented to the entry of a final judgment pursuant to which we paid the Commission a $4.0 million civil penalty to settle the Commission's claims against us. On March 31, 2016, the District Court entered a final judgment which (i) approved the settlement; (ii) permanently enjoined us from violating Section 17(a) of the Securities Act of 1933, as amended, Sections 10(b) and 13(a) of the Securities Exchange Act of 1934, as amended, and rules 10b-5, 12b-20, 13a-1, 13a-11 and 13a-13 promulgated thereunder; and (iii) ordered us to pay the agreed-to civil penalty. The Commission's action against our three former officers is still pending. We are not a party to any litigation or discussions between the SEC Staff and the former officers, and we can make no assurance regarding the outcome of that action or the Commission's claims against those individuals.

ITEM 4. Mine Safety Disclosures

Not applicable.

PART II

ITEM 5. Market for Registrant's Common Equity, Related Stockholder Matters and Issuer Purchases of Equity Securities

Market Price Information

Our common stock is traded on the NASDAQ Global Select Market under the symbol "AVEO". The following table sets forth the high and low sale prices per share for our common stock for the periods indicated:

	High	Low
2015		
First Quarter	$2.02	$0.78
Second Quarter	$3.50	$1.16
Third Quarter	$2.59	$1.14
Fourth Quarter	$1.47	$0.92

	High	Low
2016		
First Quarter	$1.27	$0.82
Second Quarter	$1.15	$0.84
Third Quarter	$1.09	$0.81
Fourth Quarter	$0.89	$0.54

Holders

As of March 17, 2017, there were approximately 57 holders of record of our common stock. We believe that the number of beneficial owners of our common stock at that date was substantially greater.

Dividends

We have never declared or paid any cash dividends on our common stock and our ability to pay cash dividends is currently prohibited by the terms of our debt financing arrangements. We currently intend to retain earnings, if any, for use in our business and do not anticipate paying cash dividends on our common stock in the foreseeable future. Payment of future dividends, if any, on our common stock will be at the discretion of our board of directors after taking into account various factors, including our financial condition, operating results, anticipated cash needs, and plans for expansion.

Purchase of Equity Securities

We did not purchase any of our equity securities during the period covered by this Annual Report on Form 10-K.

Recent Sales of Unregistered Securities

None.

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Comparative Stock Performance Graph

The information included under the heading “Comparative Stock Performance Graph” in this Item 5 of Part II of this Annual Report on Form 10-K shall not be deemed to be “soliciting material” or subject to Regulation 14A or 14C, “filed” for purposes of Section 18 of the Exchange Act, or otherwise subject to the liabilities of that section, nor shall it be deemed incorporated by reference in any filing under the Securities Act of 1933, as amended, or the Exchange Act.

The graph below matches AVEO Pharmaceuticals, Inc.’s cumulative 5-Year total shareholder return on common stock with the cumulative total returns of the NASDAQ Composite index and the NASDAQ Biotechnology index. The graph tracks the performance of a $100 investment in our common stock and in each index (with the reinvestment of all dividends) from 12/31/2011 to 12/31/2016.

The stock price performance included in this graph is not necessarily indicative of future stock price performance.

	12/11	12/12	12/13	12/14	12/15	12/16
AVEO Pharmaceuticals, Inc.	100.00	46.80	10.64	4.88	7.33	3.14
NASDAQ Composite	100.00	116.66	166.01	189.42	201.25	217.50
NASDAQ Biotechnology	100.00	134.68	232.37	307.67	328.76	262.08

ITEM 6. Selected Financial Data

The following selected consolidated financial data should be read in conjunction with our Consolidated Financial Statements and the Notes thereto and Management's Discussion and Analysis of Financial Condition and Results of Operations included elsewhere in this Annual Report on Form 10-K. The Balance Sheet Data at December 31, 2016 and 2015 and the Statement of Operations Data for each of the three years in the period ended December 31, 2016 have been derived from our audited Consolidated Financial Statements for such years, included elsewhere in this Annual Report on Form 10-K. The Balance Sheet Data at December 31, 2014, 2013 and 2012, and the Statement of Operations Data for each of the two years in the period ended December 31, 2013 have been derived from the audited Consolidated Financial Statements for such years not included in this Annual Report on Form 10-K.

Our historical results for any prior period are not necessarily indicative of results to be expected in any future period.

	Years Ended December 31,				
Statement of Operations data:	2016	2015	2014	2013	2012
	(in thousands, except per share data)				
Revenue	$2,515	$19,024	$18,123	$1,293	$19,286
Operating expenses:					
Research and development	23,703	12,875	38,254	68,468	91,358
General and administrative	8,205	14,217	18,589	28,712	36,932
Restructuring and lease exit	—	4,358	11,729	8,017	2,633
Total operating expenses	31,908	31,450	68,572	105,197	130,923
Loss from operations	(29,393)	(12,426)	(50,449)	(103,904)	(111,637)
Interest expense, net	(1,949)	(2,286)	(2,356)	(3,002)	(3,004)
Change in fair value of warrant liability	4,751	—	—	—	—
Other (expense) income	(195)	(289)	66	(123)	247
Net loss before income taxes	(26,786)	(15,001)	(52,739)	(107,029)	(114,394)
Income tax provision	(101)	—	—	—	—
Net loss	$(26,887)	$(15,001)	$(52,739)	$(107,029)	$(114,394)
Basic and diluted net loss per share	$(0.39)	$(0.27)	$(1.01)	$(2.10)	$(2.64)
Weighted average number of common shares outstanding	69,268	55,701	52,289	50,928	43,374

	Years Ended December 31,				
Balance sheet data:	2016	2015	2014	2013	2012
	(in thousands)				
Cash, cash equivalent, and marketable securities	$23,348	$34,135	$52,306	$118,506	$160,602
Working capital	15,966	27,978	18,773	97,511	151,551
Total assets	27,285	40,542	70,662	146,346	207,469
Loans payable, including current portion, net of discount	14,003	9,471	20,652	19,205	26,037
Accumulated deficit	(521,916)	(495,029)	(480,028)	(427,289)	(320,260)
Total stockholders' (deficit) equity	(1,923)	17,227	20,606	69,938	118,938

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ITEM 7. Management's Discussion and Analysis of Financial Condition and Results of Operations

You should read the following discussion and analysis of our financial condition and results of operations together with our financial statements and the related notes appearing elsewhere in this report. Some of the information contained in this discussion and analysis or set forth elsewhere in this report, including information with respect to our plans and strategy for our business and related financing, includes forward-looking statements that involve risks and uncertainties. You should read the "Risk Factors" section in Part 1—Item 1A of this report for a discussion of important factors that could cause actual results to differ materially from the results described in or implied by the forward-looking statements contained in the following discussion and analysis.

Overview

We are a biopharmaceutical company dedicated to advancing a broad portfolio of targeted therapeutics for oncology and other areas of unmet medical need. Our proprietary platform has delivered unique insights into cancer and related diseases. Our strategy is to leverage these biomarker insights and partner resources to advance the development of our clinical pipeline.

Our pipeline includes our lead candidate tivozanib, an oral, once-daily, vascular endothelial growth factor, or VEGF tyrosine kinase inhibitor, or TKI. Tivozanib is a potent, selective and long half-life inhibitor of all three VEGF receptors and is designed to optimize VEGF blockade while minimizing off-target toxicities, potentially resulting in improved efficacy and minimal dose modifications. Tivozanib has been investigated in several tumor types, including renal cell, colorectal and breast cancers.

In June 2013, the U.S. Food and Drug Administration, or FDA, issued a complete response letter denying our application for approval of the use of tivozanib in first-line treatment of advanced renal cell carcinoma, or RCC, citing concerns regarding the negative trend in overall survival in TIVO-1, our first pivotal phase 3 clinical trial.

In May 2016, we initiated enrollment and treatment of patients in TIVO-3, a new phase 3 clinical trial of tivozanib, in the third-line treatment of patients with refractory RCC seeking to address the overall survival, or OS, concerns from the TIVO-1 trial presented in the June 2013 complete response letter from the FDA and to support a request for regulatory approval of tivozanib in the United States as a third-line treatment and as a first-line treatment for RCC. We expect to complete enrollment in the TIVO-3 trial in June 2017, and to report top line data in the first quarter of 2018. The TIVO-3 trial passed an initial safety data assessment in February 2017. We expect a pre-planned interim futility analysis to occur mid-year 2017.

In March 2017, we initiated enrollment in the TiNivo trial, a phase 1/2 trial of tivozanib in combination with Opdivo®, or nivolumab, an immune checkpoint, or PD-1, inhibitor, for the treatment of RCC. Bristol-Myers Squibb is supplying nivolumab for the TiNivo trial, and we are the trial sponsor. The TiNivo trial is being led by the Institut Gustave Roussy in Paris under the direction of Professor Bernard Escudier, MD, Chairman of the Genitourinary Oncology Committee. The phase 1 trial will primarily evaluate the safety of tivozanib in combination with nivolumab at escalating doses of tivozanib and, assuming favorable results, is expected to be followed by a phase 2 expansion at the established combination dose. We expect to receive initial data from the phase 1 portion of the TiNivo trial in the first half of 2017.

In February 2016, EUSA Pharma (UK) Ltd., or EUSA, our European licensee, submitted a marketing authorization application, or MAA, for tivozanib with the European Medicines Agency, or EMA, for the treatment of RCC. The application was validated in March 2016, confirming that the submission was complete and that the EMA would initiate its review process. EUSA received the Day 120 List of Questions from the Committee for Medicinal Products for Human Use, or CHMP, of the EMA in July 2016, and submitted its responses in November 2016. In January 2017, EUSA received the Day 180 List of Outstanding Issues, or LOI, from the CHMP, of the EMA. The Day 180 LOI signifies that the MAA is not approvable at the present time, and outlines outstanding deficiencies, which are then required to be satisfactorily addressed in an oral explanation and/or in writing prior to a final application

decision. EUSA has informed AVEO that it expects to submit written responses to the Day 180 LOI in April 2017, and the EMA has tentatively scheduled EUSA to provide an oral explanation to the CHMP in May 2017.

We also have a pipeline of monoclonal antibodies, including:

(i) Ficlatuzumab, a potent hepatocyte growth factor, or HGF, antibody that inhibits the activity of the HGF/c-Met pathway. Ficlatuzumab is in early stage clinical development, with ongoing studies in acute myloid leukemia, or AML, and squamous cell cancer of the head and neck, or SCCHN. We and our worldwide partner Biodesix, Inc., or Biodesix, will share equally in all future costs and profits relating to the development of ficlatuzumab;

(ii) AV-203, a potent, high-affinity inhibitor of the ErbB3 pathway. Our partner CANbridge Life Sciences Ltd., or CANbridge, will fund manufacturing and clinical development through proof-of-concept in esophageal squamous cell carcinoma;

(iii) AV-380, a potent, humanized IgG1 inhibitory monoclonal antibody targeting growth differentiating factor-15, or GDF15, a divergent member of the TGF-ß family, for the potential treatment or prevention of cachexia. We have licensed AV-380 to Novartis, which will fund all development, manufacturing and commercialization; and

(iv) The AV-353 platform, a family of potent inhibitory antibody candidates specific to Notch 3, one of which has demonstrated an ability in preclinical models to potentially reverse disease phenotype for pulmonary arterial hypertension, or PAH. We are currently seeking a partner to advance development of the AV-353 platform for the potential treatment of PAH.

Going Concern

We have identified conditions and events that raise substantial doubt about our ability to continue as a going concern. To continue as a going concern, we must secure additional capital to provide us with additional liquidity. We believe that our approximate $23.3 million in cash, cash equivalents and marketable securities at December 31, 2016, could allow us to fund our planned operations into the fourth quarter of 2017; however, additional funds will be needed to extend these operations into 2018 and maintain compliance with our $10.0 million financial covenant under our loan agreement with Hercules Technology II, L.P. and Hercules Technology III, L.P., affiliates of Hercules Technology Growth, which we collectively refer to as Hercules. We expect that, in order to obtain additional capital, we will need to complete public or private financings of debt or equity, and / or receive milestone payments from our partners. We may also seek to procure additional funds through future arrangements with collaborators, licensees or other third parties, and these arrangements would generally require us to relinquish or encumber rights to some of our technologies or drug candidates. Moreover, we may not be able receive milestone payments or complete additional financing or enter into such arrangements on acceptable terms, if at all. For more information, refer to “—Liquidity and Capital Resources—Operating Capital Requirements and Going Concern” below and Note 1 to our consolidated financial statements included elsewhere in this Annual Report on Form 10-K.

Strategic Partnerships

CANbridge

In March 2016, which we refer to as the Effective Date, we entered into a collaboration and license agreement with CANbridge, or the CANbridge Agreement, under which we granted CANbridge the exclusive right to develop, manufacture and commercialize AV-203, our proprietary ErbB3 (HER3) inhibitory antibody, for the diagnosis, treatment and prevention of disease in humans and animals in all countries other than the United States, Canada and Mexico. Under the terms of the CANbridge Agreement, if we determine to grant a license to any ErbB3 inhibitory antibody in the United States, Canada or Mexico, we are obligated to first negotiate with CANbridge for the grant to CANbridge of a license to such rights. The parties have both agreed not to directly or indirectly develop or commercialize any other ErbB3 inhibitory antibody product during the term of the CANbridge Agreement other than pursuant to the CANbridge Agreement.

CANbridge has responsibility for all activities and costs associated with the further development, manufacture, regulatory filings and commercialization of AV-203 throughout its licensed territory. CANbridge is obligated to use commercially reasonable efforts to develop and obtain regulatory approval for AV-203 in each of China, Japan, the United Kingdom, France, Italy, Spain, and Germany. CANbridge will bear all costs for development of AV-203 through proof-of-concept in esophageal squamous cell carcinoma, after which we would expect to contribute to certain worldwide development costs.

Pursuant to the CANbridge Agreement, CANbridge paid us an upfront fee of $1.0 million in April 2016. CANbridge also agreed to reimburse us $1.0 million for certain manufacturing costs and expenses that we previously incurred, $0.5 million of which will be due on the earlier of (i) the date of validation by CANbridge of certain manufacturing development activities we conducted and (ii) twelve months from the Effective Date, and the remaining $0.5 million of which will be due on the earlier of (i) the date of validation by CANbridge of such manufacturing development activities or (ii) eighteen months from the Effective Date. We are also eligible to receive up to $42.0 million in

potential development and regulatory milestone payments and up to $90.0 million in potential sales based milestone payments based on annual net sales of licensed products. Upon commercialization, we are eligible to receive a tiered royalty, with a percentage range in the low double-digits, on net sales of approved licensed products. CANbridge's obligation to pay royalties for each licensed product expires on a country-by-country basis on the later of the expiration of patent rights covering such licensed product in such country, the expiration of regulatory data exclusivity in such country and ten years after the first commercial sale of such licensed product in such country. A percentage of any milestone and royalty payments received by us, excluding upfront and reimbursement payments, are due to Biogen Idec International GmbH, or Biogen Idec, as a sublicensing fee under our option and license agreement with Biogen dated March 18, 2009, as amended.

EUSA

In December 2015, we entered into a license agreement with EUSA under which we granted to EUSA the exclusive, sublicensable right to develop, manufacture and commercialize tivozanib in the territories of Europe (excluding Russia, Ukraine and the Commonwealth of Independent States), Latin America (excluding Mexico), Africa, Australasia and New Zealand for all diseases and conditions in humans, excluding non-oncologic diseases or conditions of the eye. EUSA is obligated to use commercially reasonable efforts to seek regulatory approval for and commercialize tivozanib throughout its licensed territories in RCC. With the exception of certain support to be provided by us in connection with the application for marketing approval by the EMA, EUSA has responsibility for all activities and costs associated with the further development, manufacture, regulatory filings and commercialization of tivozanib in its licensed territories.

Under the license agreement, EUSA made a research and development funding payment to us of $2.5 million in 2015. EUSA is required to make a further research and development funding payment of $4.0 million if the EMA grants marketing approval for tivozanib for treatment of RCC. We are eligible to receive additional research funding from EUSA, including up to $20.0 million for the data generated by our phase 3 clinical trial in third-line RCC if EUSA elects to utilize such data for regulatory or commercial purposes, and up to $2.0 million for the data generated by a phase 1 combination trial with a checkpoint inhibitor if EUSA elects to utilize such data for regulatory or commercial purposes. We would be entitled to receive milestone payments of $2.0 million per country upon reimbursement approval, if any, for RCC in each of France, Germany, Italy, Spain and the United Kingdom, and an additional $2.0 million for the grant of marketing approval, if any, in three of the following five countries: Argentina, Australia, Brazil, South Africa and Venezuela. We are also eligible to receive a payment of $2.0 million in connection with a filing by EUSA with the EMA for marketing approval, if any, for tivozanib for the treatment of each of up to three additional indications and $5.0 million per indication in connection with the EMA's grant of marketing approval for each of up to three additional indications, as well as up to $335.0 million upon EUSA's achievement of certain sales thresholds. We are also eligible to receive tiered double digit royalties on net sales, if any, of licensed products in its licensed territories ranging from a low double digit up to mid-twenty percent depending on the level of annual net sales. Thirty percent of any non-research and development related milestone and royalty payments we receive is due to Kyowa Hakko Kirin Co., Ltd. (formerly Kirin Brewery Co. Ltd.), or KHK as a sublicensing fee under our license agreement with KHK. The research and development funding payments under the EUSA license agreement are not subject to sublicensing payment to KHK.

Novartis

In August 2015, we entered into a license agreement with Novartis International Pharmaceutical Ltd., or Novartis, under which we granted Novartis the exclusive right to develop and commercialize AV-380 and our related antibodies that bind to GDF15 worldwide. Under this agreement, Novartis is responsible for all activities and costs associated with the further development, regulatory filing and commercialization of AV-380 worldwide.

Novartis made an upfront payment to us of $15.0 million in September 2015. We are also eligible to receive (a) up to $53.0 million in potential clinical milestone payments and up to $105.0 million in potential regulatory milestone payments tied to the commencement of clinical trials and to regulatory approvals of products developed under the license agreement in the United States, the European Union and Japan; and (b) up to $150.0 million in potential sales based milestone payments based on annual net sales of such products. Upon commercialization, we are eligible to receive tiered royalties on net sales of approved products ranging from the high single digits to the low double-digits. Novartis has responsibility under the license agreement for the development, manufacture and commercialization of the licensed antibodies and any resulting approved therapeutic products. In December 2015, Novartis also exercised its right under the license agreement to acquire our inventory of clinical quality drug substance, reimbursing us approximately $3.5 million for such existing inventory.

Certain milestones achieved by Novartis would trigger milestone payment obligations from us to St. Vincent's Hospital Sydney Limited, which we refer to as St. Vincent's, under our amended and restated license agreement with St. Vincent's. In addition, royalties on approved products, if any, will be payable to St. Vincent's, and we and Novartis will share that obligation equally.

Pharmstandard

In August 2015, we entered into a license agreement with JSC "Pharmstandard-Ufimskiy Vitamin Plant," or Pharmstandard, a company registered under the laws of the Russian Federation. Pharmstandard is a subsidiary of Pharmstandard OJSC. Under the license agreement, we granted to Pharmstandard the exclusive, sublicensable right to develop, manufacture and commercialize tivozanib in the territories of Russia, Ukraine and the Commonwealth of Independent States, for all diseases and conditions in humans, excluding non-oncologic ocular conditions.

In June 2016, following unsuccessful efforts to renegotiate certain terms of the Pharmstandard license agreement, Pharmstandard notified us that due to economic and market changes in Russia it was exercising its right to terminate the license

agreement effective September 9, 2016. Upon termination of the license agreement, the licenses to tivozanib granted to Pharmstandard were terminated, all product rights and regulatory documents were transferred to us, and Pharmstandard is no longer responsible for the development and commercialization of tivozanib in its licensed territories. Pharmstandard filed an application for marketing authorization in Russia for tivozanib for the treatment of renal cell carcinoma that was accepted by the Ministry of Health of the Russian Federation in February 2016. This application was withdrawn following Pharmstandard's termination notice.

Ophthotech

In November 2014, we entered into a research and exclusive option agreement with Ophthotech Corporation, or Ophthotech, pursuant to which we provided Ophthotech an exclusive option to enter into a definitive license agreement whereby we would grant Ophthotech the right to develop and commercialize tivozanib outside of Asia and the Middle East for the potential diagnosis, prevention and treatment of non-oncologic diseases or conditions of the eye in humans. Pursuant to this option agreement, we granted to Ophthotech an exclusive, royalty-free license or sublicense, as applicable, under intellectual property rights controlled by us solely to perform the research and development activities related to the use of tivozanib for the specific purposes outlined in the agreement during the option period. These activities included formulation work for ocular administration, preclinical research and the conduct of a phase 1/2a proof-of-concept clinical trial of a product containing tivozanib in patients with wet age-related macular degeneration. Ophthotech paid us $0.5 million in consideration for the grant of the option. Such amount is non-refundable and not creditable against any other amounts due under the agreement.

In January 2017, Ophthotech notified us that it will not be able to develop tivozanib and exercised its right to terminate the option agreement effective April 3, 2017.

Biodesix

In April 2014, we and Biodesix entered into the Biodesix Agreement to develop and commercialize ficlatuzumab. Under the Biodesix Agreement, we granted Biodesix perpetual, non-exclusive rights to certain intellectual property, including all clinical and biomarker data related to ficlatuzumab, to develop and commercialize VeriStrat®, Biodesix's proprietary companion diagnostic test. Biodesix granted us perpetual, non-exclusive rights to certain intellectual property, including diagnostic data related to VeriStrat, with respect to the development and commercialization of ficlatuzumab; each license includes the right to sublicense, subject to certain exceptions. Pursuant to a joint development plan, we retain primary responsibility for clinical development of ficlatuzumab. In September 2016, we and Biodesix announced the termination of the FOCAL trial, a phase 2 proof-of-concept clinical study of ficlatuzumab in which VeriStrat was used to select clinical trial subjects.

Under the Biodesix Agreement, with the exception of the costs incurred for the FOCAL trial, we and Biodesix are each required to contribute 50% of all clinical, regulatory, manufacturing and other costs to develop ficlatuzumab. Pursuant to the Biodesix Agreement, Biodesix was obligated to fund all costs of the FOCAL trial up to a cap of $15 million, following which all costs of the FOCAL trial would be shared equally. In connection with the discontinuation of the FOCAL trial, on October 14, 2016, we and Biodesix amended the Biodesix Agreement. Under the amendment, we agreed to share 50% of all program costs from August 1, 2016 forward. In return for bearing 50% of the FOCAL closeout costs after August 1, 2016, we will be entitled to recover an agreed multiple of the additional costs borne by us out of any income Biodesix receives from the partnership in connection with the licensing, development or commercialization of ficlatuzumab. We do not anticipate that these remaining costs will be material. Following such recovery, the payment structure under the original Biodesix Agreement, which generally provides that the parties share equally in any costs and revenue, will resume without such modification.

Pending marketing approval or the sublicense of ficlatuzumab, and subject to the negotiation of a commercialization agreement, each party would share equally in commercialization profits and losses, subject to our right to be the lead commercialization party.

St. Vincent's Hospital

In July 2012, we entered into a license agreement with St. Vincent's, under which we obtained an exclusive, worldwide license 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 GDF15. We believe GDF15 is a novel target for cachexia, and we are exploiting this license in our AV-380 program for cachexia. Under the agreement, we have the right to grant sublicenses subject to certain restrictions. 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.

In connection with entering into the original license agreement with St. Vincent's in July 2012, 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.

In August 2015, in connection with the execution of our license agreement with Novartis, we entered into an amended and restated agreement with St. Vincent's, pursuant to which we made an upfront payment to St. Vincent's of $1.5 million. Under our license agreement with St. Vincent's:

- We (or any sublicensee) 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 (or a sublicensee) 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 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 GDF15 or the GDF15 receptor and that is a GDF15 antagonist, and will not license or induce any other person to do the same.
- We (or any sublicensee) are required to make milestone payments, up to an aggregate total of $18.9 million, upon the earlier of achievement of specified development and regulatory milestones or a specified date for the first indication, and upon the achievement of specified development and regulatory milestones for the second and third 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;
- We (or any sublicensee) will be required to pay tiered royalty payments equal to a low-single-digit percentage of any net sales we or our sublicensees make from licensed therapeutic products, an obligation we share with Novartis equally. 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; and
- We (or any sublicensee) will be required to 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.

Astellas Pharma

In February 2011, we and our wholly-owned subsidiary AVEO Pharma Limited entered into a collaboration and license agreement with Astellas Pharma Inc. and certain of its subsidiaries pursuant to which we and Astellas intended to develop and commercialize tivozanib for the treatment of a broad range of cancers. Astellas elected to terminate the agreement effective August 2014, at which time the tivozanib rights were returned to us. In accordance with the Astellas Agreement, committed development costs, including the costs of completing certain tivozanib clinical development activities, continue to be shared equally.

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. In March 2014, we amended our agreement with Biogen Idec, and regained worldwide rights to AV-203. Pursuant to the amendment, we were

obligated to in good faith use reasonable efforts to seek a collaboration partner to fund further development and commercialization of ErbB3-targeted antibodies. We satisfied this obligation in March 2016 upon entering into our license agreement with CANbridge. We are obligated to pay Biogen Idec a percentage of milestone payments we receive under the CANbridge agreement and single-digit royalty payments on net sales related to the sale of AV-203, up to cumulative maximum amount of $50.0 million.

Kyowa Hakko Kirin

In December 2006, we entered into a license agreement with 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 and the Middle East, where KHK has retained the rights to tivozanib. 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 KHK 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.

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 a VEGF receptor.

We have upfront, milestone and royalty payment obligations to KHK under our license agreement. Upon entering into the license agreement with KHK, we made an upfront payment in the amount of $5.0 million. In March 2010, we made a milestone payment to KHK in the amount of $10.0 million in connection with the dosing of the first patient in our first phase 3 clinical trial of tivozanib (TIVO-1). In December 2012, we made a $12.0 million milestone payment to KHK in connection with the acceptance by the FDA of our 2012 new drug application, or NDA filing for tivozanib. Each milestone under the KHK agreement is a one-time only payment obligation. Accordingly, we did not owe KHK another milestone payment in connection with the dosing of the first patient in our TIVO-3 trial, and would not owe a milestone payment to KHK if we file an NDA with the FDA following the completion of our TIVO-3 clinical trial. If we obtain approval for tivozanib in the U.S., we would owe KHK a one-time milestone payment of $18.0 million, provided that we do not sublicense U.S. rights for tivozanib prior to obtaining a U.S. regulatory approval. If we were to sublicense the U.S. rights, the associated U.S. regulatory milestone would be replaced by a specified percentage of sublicensing revenue, as set forth below.

If we sublicense any of our rights to tivozanib to a third party, as we have done with EUSA pursuant to our license agreement, the sublicense defines the payment obligations of the sublicensee, which may vary from the milestone and royalty payment obligations under our KHK license relating to rights we retain. We are required to pay KHK a fixed 30% of amounts we receive from our sublicensees, including upfront license fees, milestone payments and royalties, but excluding amounts we receive in respect of research and development funding or equity investments, subject to certain limitations. In accordance with the sublicensing provisions of our KHK agreement, in 2011 we made a $22.5 million payment to KHK related to the upfront license payment received under a collaboration and license agreement we entered into with Astellas Pharmaceuticals, Inc., the termination of which became effective on August 11, 2014. If tivozanib is approved in the European Union, or EU, the $4.0 million research and development reimbursement milestone that would be owed to us by EUSA would not be subject to a sublicense revenue payment to KHK, nor would a research and development reimbursement payment upon an election by EUSA to use the data generated from our TIVO-3 or TiNivo trials for regulatory or commercial purposes, which could be up to $20.0 million for the TIVO-3 data and up to $2.0 million TiNivo data. We would, however, owe KHK 30% of other, non-research and development payments we may receive from EUSA pursuant to our license agreement, including EU reimbursement approval milestones in up to five specified EU countries, EU marketing approvals for up to three additional indications beyond RCC, marketing approvals in up to three specified licensed territories outside of the EU, sales-based milestones and royalties, as set forth above.

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.

The license agreement will remain in effect until the expiration of all of our royalty and sublicense revenue obligations to KHK, determined on a product-by-product and country-by-country basis, unless we elect 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, KHK can terminate the agreement, resulting in a loss of our rights to tivozanib and an obligation to assign or license to KHK any intellectual property or other rights we may have in tivozanib, including our regulatory filings, regulatory approvals, patents and trademarks for tivozanib.

Financial Overview

We do not have a history of being profitable and, as of December 31, 2016, we had an accumulated deficit of $521.9 million. We anticipate that we will continue to incur significant operating costs over the next several years as we continue our planned development activities for our preclinical and clinical products. We will need additional funding to support our operating activities, and the timing and nature of activities contemplated for 2017 and thereafter will be conducted subject to the availability of sufficient financial resources. Refer to the "—Going Concern" and "Liquidity and Capital Resources—Operating Capital Requirements and Going Concern" sections for a further discussion of our funding requirements.

Revenue

To date, we have not generated any revenue from product sales. All of our revenue to date has been derived from license fees, milestone payments, premium over the fair value of convertible preferred shares sold to our strategic partners, and research and development payments received from our strategic partners.

In the future, we may generate revenue from a combination of product sales, license fees, milestone payments and research and development payments in connection with strategic partnerships, and royalties resulting from the sales of products developed under licenses of our intellectual property. We expect that any revenue we generate will fluctuate from quarter to quarter as a result of the timing and amount of license fees, research and development reimbursements, milestone and other payments received under our strategic partnerships, and the payments that we receive upon the sale of our products, to the extent any are successfully commercialized. We do not expect to generate revenue from product sales in the near term. If we or our strategic partners fail to complete the development of our drug candidates in a timely manner or obtain regulatory approval for them, our ability to generate future revenue, and our results of operations and financial position, would be materially adversely affected.

Research and Development Expenses

Research and development expenses have historically consisted of expenses incurred in connection with the discovery and development of our product candidates. We recognize research and development expenses as they are incurred. These expenses consist primarily of:

- employee-related expenses, which include salaries, benefits and stock-based compensation expense;
- expenses incurred under agreements with contract research organizations, investigative sites and consultants that conduct our clinical trials and a substantial portion of our preclinical studies;
- the cost of acquiring and manufacturing drug development related materials;
- the cost of completing certain tivozanib clinical development activities that were initiated as part of our prior partnership with Astellas;
- facilities, depreciation and other allocated expenses, which include direct and allocated expenses for rent and maintenance of facilities and equipment, and depreciation of fixed assets;
    - license fees for, and milestone payments related to, in-licensed products and technology; and
- costs associated with outsourced development activities, regulatory approvals and medical affairs

Research and development expenses are net of amounts reimbursed under our agreements with Astellas and Biodesix for Astellas' and Biodesix' respective shares of development costs incurred by us under our joint development plans with each respective partner.

We expect that research and development expenses in 2017 will remain at current levels as we seek to advance and complete enrollment in the TIVO-3 trial and the TiNivo trial.

We track external development expenses and personnel expense on a program-by-program basis and allocate common expenses, such as scientific consultants and laboratory supplies, to each program based on the personnel resources allocated to such program. Facilities, depreciation, stock-based compensation, research and development management and research and development support services are not allocated among programs and are considered overhead. Below is a summary of our research and development expenses for the years ended December 31, 2016, 2015 and 2014, respectively:

	Years Ended December 31,			2016 / 2015 Comparison		2015 / 2014 Comparison	
	2016	2015	2014	$	%	$	%
	($ in thousands)						
Tivozanib	$21,231	$8,513	$9,530	$12,718	149 %	$(1,017)	(11)%
AV-380 Program in Cachexia	464	2,408	12,968	(1,944)	(81)%	(10,560)	(81)%
Ficlatuzumab	746	80	1,579	666	833 %	(1,499)	(95)%
AV-203	76	532	1,843	(456)	(86)%	(1,311)	(71)%
Other pipeline programs	—	11	72	(11)	(100)%	(61)	(85)%
Other research and development	—	10	67	(10)	(100)%	(57)	(85)%
Overhead	1,186	1,321	12,195	(135)	(10)%	(10,874)	(89)%
Total research and development expenses	$23,703	$12,875	$38,254	$10,828	84 %	$(25,379)	(66)%

Tivozanib

We have pursued partnering options to fund further tivozanib development in appropriate clinical settings outside of our strategic focus. Our licensee, EUSA, has submitted an application for marketing authorization for tivozanib for the treatment of RCC to the EMA. EUSA is responsible for all activities and costs associated with the further development and commercialization of tivozanib within its licensed territories, excluding non-oncologic diseases or conditions of the eye. We continue to share the costs of development activities to which we and Astellas were committed at the time the Astellas partnership was terminated.

In May 2016, we initiated TIVO-3, an additional phase 3 trial of tivozanib vs. sorafenib. TIVO-3, which is expected to enroll approximately 322 patients in the refractory RCC setting, will use progression-free survival, or PFS, as the primary endpoint and OS as a secondary endpoint, and is designed to address the OS concerns presented in the June 2013 complete response letter from the FDA and to support a request for approval of tivozanib as a third-line treatment and as a first-line treatment. We expect the total estimated remaining costs of this trial, including drug supply and distribution, to be approximately $22.0 million to $25.0 million through completion. We have also initiated the TiNivo trial in collaboration with Bristol-Myers Squibb, or BMS, which is providing nivolumab for the study. We are the study sponsor. The TiNivo trial is a phase 1/2 trial of tivozanib in combination with nivolumab, a PD-1 inhibitor, for the treatment of RCC, for which our costs, including tivozanib drug supply and distribution, could be in the range of $2.0 million to $2.5 million.

AV-380 Program in Cachexia

In August 2015, we entered into a license agreement with Novartis, under which we granted Novartis the exclusive right to develop and commercialize AV-380 and related AVEO antibodies that bind to GDF15 worldwide. Under this agreement, Novartis is responsible for all activities and costs associated with the further development, regulatory filing and commercialization of AV-380 worldwide. We do not expect to incur any significant costs related to AV-380 in future periods beyond any milestone fees and royalties payable to St.Vincent's pursuant to our in-licensing agreement, which comprises substantially all of the costs incurred during the year ended December 31, 2016.

AV-203

In March 2014, we regained our worldwide rights from Biogen Idec to develop, manufacture and commercialize AV-203. In March 2016, we entered into a collaboration and license agreement with CANbridge, under which we granted CANbridge the exclusive right to develop and commercialize AV-203 in all countries other than the United States, Canada and Mexico. CANbridge is responsible for all costs of developing and commercializing AV-203 within its licensed territory. For a period of time following the completion of certain proof-of-concept clinical studies by CANbridge involving the use of AV-203 for the treatment of squamous cell esophagus cancer, we agreed to negotiate exclusively with CANbridge for (a) the right to co-develop ErbB3 inhibitory antibody products for the treatment of squamous cell esophagus cancer or (b) the right to include the United States, Canada and Mexico as part of the licensed territories. We do not expect to incur any significant costs related to AV-203 prior to CANbridge's completion of a proof-of-concept clinical study.

Ficlatuzumab

In April 2014, we entered into the Biodesix Agreement to develop and commercialize ficlatuzumab, our potent HGF inhibitory antibody. Pursuant to the agreement, Biodesix was to provide up to $15.0 million for the phase 2 FOCAL trial of ficlatuzumab in combination with erlotinib in first-line advanced non-small cell lung cancer patients selected using Biodesix's proprietary companion diagnostic VeriStrat. In connection with the discontinuation of the FOCAL trial, on October 14, 2016 we and Biodesix amended the Biodesix Agreement. Under the amendment, we agreed to fund 50% of the shutdown costs of the FOCAL trial after August 1, 2016. In return, we would be entitled to reimbursement at a multiple of such shutdown expenses out of any future revenues Biodesix receives from ficlatuzumab. All manufacturing and all non-FOCAL development, regulatory or commercial expenses for ficlatuzumab will continue to be equally shared, as provided in the original Biodesix Agreement. Due to the unpredictable nature of clinical development, we are unable to estimate with any certainty the costs we will incur in the future development of ficlatuzumab.

Uncertainties of Estimates Related to Research and Development Expenses

The process of conducting preclinical studies and clinical trials necessary to obtain FDA approval for each of our product candidates is costly and time-consuming. The probability of success for each product candidate and clinical trial may be affected by a variety of factors, including, among others, the quality of the product candidate's early clinical data, investment in the program, competition, manufacturing capabilities and commercial viability.

At this time, we cannot reasonably estimate or know the nature, specific timing and estimated costs of the efforts that will be necessary to complete the development of our product candidates, or the period, if any, in which material net cash inflows may commence from sales of any approved products. This uncertainty is due to the numerous risks and uncertainties associated with developing drugs, including the uncertainty of:

- our ability to establish and maintain strategic partnerships, the terms of those strategic partnerships and the success of those strategic partnerships, if any, including the timing and amount of payments that we might receive from strategic partners;
- the scope, progress, results and costs of preclinical development, laboratory testing and clinical trials for any product candidate;
- the progress and results of our clinical trials;
- the costs, timing and outcome of regulatory review of our product candidates;
- the emergence of competing technologies and products and other adverse market developments; and
- the costs of preparing, filing and prosecuting patent applications and maintaining, enforcing and defending intellectual property-related claims.

As a result of the uncertainties associated with developing drugs, including those discussed above, we are unable to determine the duration and completion costs of current or future clinical stages of our product candidates, or when, or to what extent, we will generate revenues from the commercialization and sale of any of our product candidates. Development timelines, probability of success and development costs vary widely. We anticipate that we will make determinations as to which additional programs to pursue and how much funding to direct to each program on an ongoing basis in response to the scientific and clinical success, if any, of each product candidate, as well as ongoing assessment of each product candidate's commercial potential. We will need to raise substantial additional capital in the future in order to fund the development of our preclinical and clinical product candidates.

General and Administrative Expenses

General and administrative expenses consist principally of salaries and related costs for personnel in executive, finance, corporate development, information technology, legal and human resource functions. Other general and administrative expenses include facility costs not otherwise included in research and development expenses, patent filing, prosecution and defense costs and professional fees for legal, consulting, pre-commercialization activities,

auditing and tax services. We anticipate that our general and administrative expenses in 2017 will remain at current levels.

Warrants Issued in Connection with Private Placement

We account for warrant instruments that either conditionally or unconditionally obligate the issuer to transfer assets as liabilities regardless of the timing of the redemption feature or price, even though the underlying shares may be classified as permanent or temporary equity. These warrants are subject to revaluation at each balance sheet date, and any changes in fair value are recorded as a non-cash component of other expense, until the earlier of their exercise or expiration or upon the completion of a liquidation event.

Interest Expense, Net

Interest income consists of interest earned on our cash, cash equivalents and marketable securities. The primary objective of our investment policy is capital preservation. Interest expense consists of interest, amortization of debt discount, and amortization of deferred financing costs associated with our loans payable.

Income Taxes

We calculate our provision for income taxes on ordinary income based on our projected annual tax rate for the year. We recorded a loss for the years ended December 31, 2016, 2015, and 2014, and since we maintain a full valuation allowance on all of our deferred tax assets, we have recorded no income tax provision or benefit during the years ended December 31, 2016, 2015, and 2014, except for a $0.1 million provision recorded in the year ended December 31, 2016 related to withholding taxes incurred in a foreign jurisdiction.

Critical Accounting Policies and Significant Judgments and Estimates

Our discussion and analysis of our financial condition and results of operations are based on our Consolidated Financial Statements and the notes thereto included elsewhere in this Annual Report on Form 10-K, which have been prepared in accordance with accounting principles generally accepted in the United States. The preparation of these financial statements requires us to make estimates and judgments that affect the reported amounts of assets, liabilities, revenues and expenses and the disclosure of contingent assets and liabilities in our financial statements. On an ongoing basis, we evaluate our estimates and judgments, including those related to revenue recognition, accrued clinical expenses, and stock-based compensation. We base our estimates on historical experience, known trends and events and various other factors that we and our management believe to be reasonable under the circumstances, the results of which form the basis for making judgments about the carrying values of assets and liabilities that are not readily apparent from other sources. Actual results may differ from these estimates under different assumptions or conditions.

Revenue Recognition

Our revenues have historically been generated primarily through collaborative research, development and commercialization agreements. The terms of these agreements generally contain multiple elements, or deliverables, which may include (i) licenses, or options to obtain licenses, to our technology, (ii) research and development activities to be performed on behalf of the collaborative partner, and (iii) in certain cases, services in connection with the manufacturing of pre-clinical and clinical material. Payments to us under these arrangements typically include one or more of the following: non-refundable, upfront license fees; option exercise fees; funding of research and/or development efforts; milestone payments; and royalties on future product sales.

When evaluating multiple element arrangements, we consider whether the deliverables under the arrangement represent separate units of accounting. This evaluation requires subjective determinations and requires management to make judgments about the individual deliverables and whether such deliverables are separable from the other aspects of the contractual relationship. In determining the units of accounting, management evaluates certain criteria, including whether the deliverables have standalone value, based on the relevant facts and circumstances for each arrangement. The consideration received is allocated among the separate units of accounting using the relative selling price method, and the applicable revenue recognition criteria are applied to each of the separate units.

We determine the estimated selling price for deliverables within each agreement using vendor-specific objective evidence, or VSOE, of selling price, if available, third-party evidence, or TPE, of selling price if VSOE is not available, or best estimate of selling price if neither VSOE nor TPE is available. Determining the best estimate of selling price for a deliverable requires significant judgment. We typically use best estimates of selling price to estimate the selling price for licenses to our proprietary technology, since we often do not have VSOE or TPE of

selling price for these deliverables. In those circumstances where we utilize the best estimate of selling price to determine the estimated selling price of a license to our proprietary technology, we consider market conditions as well as entity-specific factors, including those factors contemplated in negotiating the agreements and internally developed models that include assumptions related to the market opportunity, estimated development costs, probability of success and the time needed to commercialize a product candidate pursuant to the applicable license. In validating our best estimate of selling price, we evaluate whether changes in the key assumptions used to determine the best estimate of selling price will have a significant effect on the allocation of arrangement consideration among multiple deliverables.

We typically receive non-refundable, upfront payments when licensing our intellectual property in conjunction with a research and development agreement. When management believes the license to our intellectual property does not have stand-alone value from the other deliverables to be provided in the arrangement, we generally recognize revenue attributed to the license on a straight-line basis over our contractual or estimated performance period, which is typically the term of our research and development obligations. If management cannot reasonably estimate when our performance obligation ends, then revenue is deferred until management can

reasonably estimate when the performance obligation ends. When management believes the license to our intellectual property has stand-alone value, we generally recognize revenue attributed to the license upon delivery. The periods over which revenue should be recognized are subject to estimates by management and may change over the course of the research and development agreement. Such a change could have a material impact on the amount of revenue we record in future periods.

Payments or reimbursements resulting from our research and development efforts for those arrangements where such efforts are considered as deliverables are recognized as the services are performed and are presented on a gross basis so long as there is persuasive evidence of an arrangement, the fee is fixed or determinable, and collection of the related receivable is reasonably assured. Amounts received prior to satisfying the above revenue recognition criteria are recorded as deferred revenue in the accompanying balance sheets.

At the inception of each agreement that includes milestone payments, we evaluate whether each milestone is substantive and at risk to both parties on the basis of the contingent nature of the milestone. This evaluation includes an assessment of whether (a) the consideration is commensurate with either (1) the entity's performance to achieve the milestone, or (2) the enhancement of the value of the delivered item(s) as a result of a specific outcome resulting from the entity's performance to achieve the milestone, (b) the consideration relates solely to past performance, and (c) the consideration is reasonable relative to all of the deliverables and payment terms within the arrangement. We evaluate factors such as the scientific, regulatory, commercial and other risks that must be overcome to achieve the respective milestone, the level of effort and investment required to achieve the respective milestone and whether the milestone consideration is reasonable relative to all deliverables and payment terms in the arrangement in making this assessment.

We aggregate our milestones into four categories: (i) clinical and development milestones, (ii) regulatory milestones, (iii) commercial milestones, and (iv) patent-related milestones. Clinical and development milestones are typically achieved when a product candidate advances into a defined phase of clinical research or completes such phase. For example, a milestone payment may be due to us upon the initiation of a phase 3 clinical trial for a new indication, which is the last phase of clinical development and could eventually contribute to marketing approval by the FDA or other global regulatory authorities. Regulatory milestones are typically achieved upon acceptance of the submission for marketing approval of a product candidate or upon approval to market the product candidate by the FDA or other global regulatory authorities. For example, a milestone payment may be due to us upon the FDA's acceptance of a New Drug Application, or NDA. Commercial milestones are typically achieved when an approved pharmaceutical product reaches certain defined levels of net sales by the licensee, such as when a product first achieves global sales or annual sales of a specified amount. Patent-related milestones are typically achieved when a patent application is filed or a patent is issued with respect to certain intellectual property related to the applicable collaboration.

Revenues from clinical and development, regulatory, and patent-related milestone payments, if the milestones are deemed substantive and the milestone payments are nonrefundable, are recognized upon successful accomplishment of the milestones. We have concluded that the clinical and development, regulatory and patent-related milestones pursuant to our current research and development arrangements are substantive. Milestones that are not considered substantive are accounted for as license payments and recognized on a straight-line basis over the remaining period of performance. Revenues from commercial milestone payments are accounted for as royalties and are recorded as revenue upon achievement of the milestone, assuming all other revenue recognition criteria are met.

Accrued Expenses and Accrued Clinical Trial Costs and Contract Research Liabilities

As part of the process of preparing our financial statements, we are required to estimate accrued expenses. This process involves identifying services which have been performed on our behalf, and estimating the level of service performed and the associated cost incurred for such service as of each balance sheet date in our financial statements. Given our current business, the primary area of uncertainty concerning accruals which could have a material effect on our operating results is with respect to service fees paid to contract manufacturers in conjunction with the production

of clinical drug supplies and to contract research organizations in connection with our clinical trials. In connection with all of the foregoing service fees, our estimates are most affected by our understanding of the status and timing of services provided. The majority of our service providers, including contract research organizations, invoice us in arrears for services performed. In the event that we do not identify some costs which have begun to be incurred, or we under or overestimate the level of services performed or the costs of such services in a given period, our reported expenses for such period would be understated or overstated. We currently reflect the effects of any changes in estimates based on changes in facts and circumstances directly in our operations in the period such change becomes known.

Our arrangements with contract research organizations in connection with clinical trials often provide for payment prior to commencing the project or based upon predetermined milestones throughout the period during which services are expected to be performed. We recognize expense relating to these arrangements based on the various services provided over the estimated time to completion. The date on which services commence, the level of services performed on or before a given date, and the cost of such services are often determined based on subjective judgments. We make these judgments based upon the facts and circumstances

known to us based on the terms of the contract and our ongoing monitoring of service performance. During the years ended December 31, 2016, 2015 and 2014, we had arrangements with multiple contract research organizations whereby these organizations commit to performing services for us over multiple reporting periods. We recognize the expenses associated with these arrangements based on our expectation of the timing of the performance of components under these arrangements by these organizations. Generally, these components consist of the costs of setting up the trial, monitoring the trial, closing the trial and preparing the resulting data. Costs related to patient enrollment in clinical trials are accrued as patients are enrolled in the trial.

With respect to financial reporting periods presented in this Annual Report on Form 10-K, and based on our receipt of invoices from our third party providers, the timing of our actual costs incurred have not differed materially from our estimated timing of such costs. In light of the foregoing, we do not believe our practices for estimating future expenses and making judgments concerning the accrual of expenses are reasonably likely to change in the future.

Stock-Based Compensation

Under our stock-based compensation programs, we periodically grant stock options and restricted stock to employees, directors and nonemployee consultants. We also issue shares under an employee stock purchase plan. The fair value of all awards is recognized in our statements of operations over the requisite service period for each award.

Awards that vest as the recipient provides service are expensed on a straight-line basis over the requisite service period. Other awards, such as performance-based awards that vest upon the achievement of specified goals, are expensed using the accelerated attribution method if achievement of the specified goals is considered probable. We have also granted awards that vest upon the achievement of market conditions. Per Accounting Standards Codification, or ASC, 718 Share-Based Payments, market conditions must be considered in determining the estimated grant-date fair value of share-based payments and the market conditions must be considered in determining the requisite service period over which compensation cost is recognized. We estimate the fair value of the awards with market conditions using a Monte Carlo simulation, which utilizes several assumptions including the risk-free interest rate, the volatility of our stock and the exercise behavior of award recipients. The grant-date fair value of the awards is then recognized over the requisite service period, which represents the derived service period for the awards as determined by the Monte Carlo simulation.

We use the Black-Scholes option pricing model to value our stock option awards without market conditions, which requires us to make certain assumptions regarding the expected volatility of our common stock price, the expected term of the option grants, the risk-free interest rate and the dividend yield with respect to our common stock. In 2016, we began calculating volatility using our historical data. Previously, we did not have sufficient history to support a calculation of volatility using only our historical data. As such, prior to 2016, we used a weighted-average volatility considering our own volatility since March 2010 and the volatilities of several peer companies. For purposes of identifying similar entities, we considered characteristics such as industry, length of trading history, similar vesting terms and in-the-money option status. Due to a lack of our own historical data, we elected to use the “simplified” method for “plain vanilla” options to estimate the expected term of our stock option grants. Under this approach, the weighted-average expected life is presumed to be the average of the vesting term and the contractual term of the option. The risk-free interest rate used for each grant is based on the U.S. Treasury yield curve in effect at the time of grant for instruments with a similar expected life. We utilize a dividend yield of zero based on the fact that we have never paid cash dividends and have no present intention to pay cash dividends.

The fair value of equity-classified awards to employees and directors are measured at fair value on the date the awards are granted. Awards to nonemployee consultants are recorded at their fair values and are re-measured as of each balance sheet date until the recipient’s services are complete.

During the years ended December 31, 2016, 2015 and 2014, respectively, the assumptions used in the Black-Scholes pricing model for new grants were as follows:

	Years Ended December 31,		
	2016	2015	2014
Volatility factor	72.18% - 74.47%	77.04% - 78.70%	69.38% - 77.92%
Expected term (in years)	3.00 - 6.25	5.50 - 6.25	5.50 - 6.25
Risk-free interest rates	1.07% - 2.01%	1.54% - 1.93%	1.81% - 2.02%
Dividend yield	—	—	—

We recognized stock-based compensation expense of approximately $1.0 million, $1.1 million and $2.8 million for the years ended December 31, 2016, 2015, and 2014, respectively. During the years ending December 31, 2016, 2015 and 2014, we estimated our expected forfeiture rates to be 76%, 71% and 62%, respectively. As of December 31, 2016, we had approximately $0.8 million of

total unrecognized stock-based compensation expense for stock options, which we expect to recognize over a weighted-average period of approximately 2.5 years.

We record compensation expense only for those awards that we ultimately expect will vest. We have performed an historical analysis of option awards that were forfeited prior to vesting and recorded total stock option expense that reflected this estimated forfeiture rate. We cannot currently predict the total amount of stock-based compensation expense to be recognized in any future period because such amounts will depend on levels of stock-based payments granted in the future as well as the portion of the awards that actually vest. Forfeitures are estimated each period and adjusted if actual forfeitures differ from those estimates. Actual forfeitures may differ from our estimates as a result of significant changes in our operations.

We have historically granted stock options at exercise prices that are not less than the fair market value of our common stock.

Warrants Issued in Connection with Private Placement

We account for warrant instruments that either conditionally or unconditionally obligate the issuer to transfer assets as liabilities regardless of the timing of the redemption feature or price, even though the underlying shares may be classified as permanent or temporary equity. In May 2016, we issued warrants to purchase an aggregate of 17,642,482 shares of our common stock in connection with a private placement financing and recorded the warrants as a liability. See "—Liquidity and Capital Resources—Private Placement/PIPE Warrants" below. The fair value of these warrants has been determined using the Black-Scholes pricing model. These warrants are subject to revaluation at each balance sheet date, and any changes in fair value are recorded as a non-cash component of other income (expense), net in our Statements of Operations until the earlier of their exercise or expiration or upon the completion of a liquidation event.

The key assumptions used to value the PIPE Warrants were as follows:

	Original Issuance	December 31, 2016
Expected price volatility	76.25%	78.18%
Expected term (in years)	5.00	4.50
Risk-free interest rates	1.22%	1.93%
Stock price	$ 0.89	$ 0.54
Dividend yield	—	—

Results of Operations

Comparison of Years Ended December 31, 2016, 2015 and 2014

Revenues

	Years Ended December 31,			2016 / 2015 Comparison		2015 / 2014 Comparison	
	2016	2015	2014	$	%	$	%
Strategic Partner:	($ in thousands)						

Novartis	$—	$18,450	$—	$(18,450)	(100)%	$18,450	100%
CANbridge	1,028	—	—	1,028	100%	0	-%
EUSA	395	14	—	381	2721%	14	100%
Biogen Idec	38	268	14,520	(230)	(86)%	(14,252)	(98)%
Pharmstandard	939	61	—	878	1439%	61	100%
Astellas	—	—	3,564	—	-%	(3,564)	(100)%
Ophthotech	115	231	39	(116)	(50)%	192	492%
Total revenues	$2,515	$19,024	$18,123	$(16,509)	(87)%	$901	5%

In 2016 as compared to 2015, revenue decreased by $16.5 million, principally due to $18.5 million in revenue that was recognized in 2015 related to Novartis for the $15.0 million upfront payment received in connection with our licensing agreement entered into in August 2015 and $3.5 million for the purchase of our inventory of clinical material in the fourth quarter of 2015. This decrease was partially offset by the $1.0 million upfront payment received in connection with our collaboration and license agreement with CANbridge entered into in March 2016 and $0.8 million in the acceleration of deferred revenue that was recognized upon the effective termination of our licensing agreement with Pharmstandard in September 2016 that otherwise would have been recognized over the performance period through April 2022.

In 2015 as compared to 2014, revenue increased by $0.9 million principally due to the recognition of $18.5 million of revenue associated with the receipt of a $15.0 million upfront payment for our license of AV-380 to Novartis and Novartis' subsequent purchase of clinical material for $3.5 million. These amounts were partially offset by a decrease of $3.6 million of revenue from Astellas following the termination of our collaboration agreement in 2014 and a decrease of $14.3 million of revenue recognized from our arrangement with Biogen due to the one-time recognition of previously deferred revenue following an amendment to our agreement in 2014.

Research and Development Expenses

	Years Ended December 31,			2016 / 2015 Comparison		2015 / 2014 Comparison	
	2016	2015	2014	$	%	$	%
	($ in thousands)						
Tivozanib	$21,231	$8,513	$9,530	$12,718	149 %	$(1,017)	(11)%
AV-380 Program in Cachexia	464	2,408	12,968	(1,944)	(81)%	(10,560)	(81)%
Ficlatuzumab	746	80	1,579	666	833 %	(1,499)	(95)%
AV-203	76	532	1,843	(456)	(86)%	(1,311)	(71)%
Other pipeline programs	—	11	72	(11)	(100)%	(61)	(85)%
Other research and development	—	10	67	(10)	(100)%	(57)	(85