AVEO PHARMACEUTICALS INC
Form 10-K
March 14, 2019

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, 2018

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 Capital 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 every Interactive Data File required to be submitted 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 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, a smaller reporting company, or emerging growth company. See definitions of "large accelerated filer," "accelerated filer," "smaller reporting company," and "emerging growth company" in Rule 12b-2 of the Exchange Act.

Large accelerated filer	Accelerated filer
Non-accelerated filer	Smaller reporting company
	Emerging growth company

If an emerging growth company, indicate by check mark if the registrant has elected not to use the extended transition period for complying with any new or revised financial accounting standards provided pursuant to Section 13(a) of the Exchange Act.

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, held by non-affiliates of the registrant, based on the last reported sale price of the common stock on the Nasdaq Capital Market at the close of business on June 29, 2018, was $204,881,812.

The number of shares outstanding of the registrant's Common Stock as of March 8, 2019 were 139,000,340.

Documents incorporated by reference:

Portions of our definitive proxy statement for our 2019 annual meeting of stockholders are incorporated by reference into Part III of this Annual Report on Form 10-K.

AVEO PHARMACEUTICALS, INC.

TABLE OF CONTENTS

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.

Cautionary Note Regarding Forward-Looking Statements and Industry Data

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,” “might,” “plan,” “project,” “should,” “target,” “will,” “would” or other words that convey uncertainty of future events o outcomes to 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, 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, including as it relates to the TIVO-3 trial and tivozanib;
- our ability to successfully file a new drug application, or NDA, with the U.S. Food and Drug Administration, or the FDA, for tivozanib on the timeline we anticipate, or at all;
- our ability to enter into and maintain our third-party collaboration agreements and our ability, and the ability of our strategic partners, to achieve development and commercialization objectives under these arrangements;
- the timing and costs of any product candidate seeking and obtaining regulatory approval;
- our ability, and the ability of our collaborators, to successfully enroll and complete clinical trials;
- our ability to maintain compliance with regulatory requirements applicable to our product candidates;
- our ability to obtain and maintain adequate protection for intellectual property rights relating to our product candidates;
- our ability to successfully implement our strategic plans;
    - our ability to raise the substantial additional funds required to achieve our goals, including those goals pertaining to the development and commercialization of tivozanib;
- unplanned capital requirements;

3

- adverse general economic and industry conditions;
- 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.

This report also includes statistical and other industry and market data that we obtained from industry publications and research, surveys and studies conducted by third parties. All of the market data used in this report involves a number of assumptions and limitations, and you are cautioned not to give undue weight to such data. We believe that the information from these industry publications, surveys and studies is reliable. The industry in which we operate is subject to a high degree of uncertainty and risk due to a variety of important factors, including those discussed under the heading “Risk Factors” in Part I, Item 1A of this report. These and other factors could cause results to differ materially from those expressed in the estimates made by the independent parties and by us.

PART I

ITEM 1. Business

Overview

We are a biopharmaceutical company seeking to advance targeted medicines for oncology and other unmet medical needs. We are working to develop and commercialize our lead candidate tivozanib in North America as a treatment for advanced or metastatic renal cell carcinoma, or RCC. In November 2018, we announced that our phase 3 randomized, controlled, multi-center, open-label trial comparing tivozanib to an approved therapy, sorafenib (Nexavar®), in 350 subjects as a third- and fourth-line treatment for RCC, including subjects with prior checkpoint inhibitor therapy, which we refer to as the TIVO-3 trial, met its primary endpoint of progression-free survival, or PFS. Data for the secondary endpoint of the TIVO-3 trial, overall survival, or OS, was not mature as of the time of the final PFS analysis. In January 2019, the U.S. Food and Drug Administration, or FDA, recommended that we not submit a new drug application, or NDA, for tivozanib at this time as the preliminary OS results from the TIVO-3 trial did not allay its concerns about a potential detriment in OS from our previously completed phase 3 trial for tivozanib in the first-line treatment of RCC, which we refer to as the TIVO-1 trial. Following discussion with the FDA, we have extended the timeline for the TIVO-3 trial OS analysis and plan to conduct another interim OS analysis in August 2019. We anticipate reporting the results of this analysis in the fourth quarter of 2019, and plan to provide an update regarding the potential submission of an NDA for tivozanib to the FDA.

We are leveraging several collaborations in the development of tivozanib. We have sublicensed tivozanib, marketed under the brand name FOTIVDA®, for oncological indications in Europe and other territories outside of North America. Through our partner, tivozanib is approved in the European Union, or EU, as well as Norway and Iceland, for the first-line treatment of adult patients with RCC and for adult patients who are vascular endothelial growth factor receptor, or VEGFR, and mTOR pathway inhibitor-naïve following disease progression after one prior treatment with cytokine therapy for RCC. We also have clinical collaborations to study tivozanib in combination with immune checkpoint inhibitors in RCC and in hepatocellular carcinoma, or HCC. We are conducting a phase 2 clinical trial of tivozanib in combination with Opdivo® (nivolumab), a PD-1 inhibitor, in the first-line and the second-line treatment of RCC, which we refer to as the TiNivo trial. Leveraging early monotherapy results in HCC, we have a clinical collaboration to study tivozanib in combination with IMFINZI® (durvalumab), a PD-L1 inhibitor, for the treatment of advanced, unresectable HCC. In addition, a new formulation of tivozanib is in pre-clinical development for the treatment of age-related macular degeneration.

As part of our strategy, we have also entered into partnerships to help fund the development and commercialization of our other product candidates. Ficlatuzumab, a hepatocyte growth factor, or HGF, inhibitory antibody, is currently being tested in several investigator sponsored studies jointly funded by us and one of our development partners for the potential treatment of squamous cell carcinoma of the head and neck, or HNSCC, acute myeloid leukemia, or AML, and pancreatic cancer. Our partner for AV-203, an anti-ErbB3 monoclonal antibody, is planning to initiate clinical studies in China in 2019 in esophageal squamous cell carcinoma, or ESCC, and has committed to funding the development of AV-203 through proof-of-concept. We have recently regained the rights to AV-380, a humanized IgG1 inhibitory monoclonal antibody targeting growth differentiation factor 15, or GDF15, a divergent member of the TGF-ß family, for the potential treatment of cancer cachexia, and are working to initiate preclinical toxicology studies mid-2019 to support the potential filing of an investigational new drug application, or IND, with the FDA. We are evaluating options for the development of our preclinical AV-353 platform which targets the Notch 3 pathway.

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 funding to support our current operating plan. As of December 31, 2018, we had approximately $24.4 million in cash, cash equivalents and marketable securities. In February 2019, we sold approximately 12.5 million shares of our common stock pursuant to our sales agreement with

SVB Leerink, or the Leerink Sales Agreement, and received approximately $7.5 million in net proceeds. Based on our available cash resources, we do not have sufficient cash on hand to support current operations for at least the next twelve months from the date of filing this Annual Report on Form 10-K. This condition raises substantial doubt about our ability to continue as a going concern. We expect that, in order to obtain additional funding, we will need to receive additional milestone payments and royalties from our partners and / or complete additional public or private financings of debt or equity. 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. We may not receive milestone payments or be able to complete financings or enter into third-party arrangements on acceptable terms, if at all. For more information, 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—Liquidity and Going Concern" below and Note 1, "—Liquidity and Going Concern" of the Notes to our consolidated financial statements included elsewhere in this Annual Report on Form 10-K.

Our Product Candidates

Tivozanib

Our pipeline includes our lead candidate tivozanib, an oral, once-daily, VEGFR 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, hepatocellular, colorectal and breast cancers, as well as in age-related macular degeneration. We have 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. We have sublicensed to EUSA Pharma (UK) Limited, or EUSA, the right to develop and commercialize tivozanib in our licensed territories outside of North America, including Europe (excluding Russia, Ukraine and the Commonwealth of Independent States), Latin America (excluding Mexico), Africa and Australasia. The EUSA sublicense excludes non-oncologic ocular conditions, to which we have retained development rights in all of our licensed territories. We are planning further development of tivozanib as a combination therapy with immune checkpoint inhibitors for the treatment of RCC and HCC.

Clinical and Regulatory Development in RCC

First-Line Phase 3 Trial (TIVO-1): We conducted the TIVO-1 trial, a global phase 3 clinical trial comparing the efficacy and safety of tivozanib with sorafenib, an approved therapy, for the first-line treatment of RCC. The trial met its primary endpoint for PFS with a median PFS in the tivozanib arm of 11.9 months compared with 9.1 months in the sorafenib arm. The trial also showed significant improvement in overall response rate, or ORR, of 33.1% for tivozanib versus 23.3% for sorafenib. The trial showed a favorable tolerability profile for tivozanib, as evidenced by fewer dose interruptions and dose reductions than sorafenib. However, the trial showed a non-statistically significant trend favoring the sorafenib treatment group in OS. The protocol-specified final OS analysis at 24 months since the last patient enrolled showed a median OS for the tivozanib arm of 28.8 months versus a median OS for the sorafenib arm of 29.3 months (hazard ratio (HR)=1.245, p=0.105). Subsequently, in connection with EUSA's application for the use of tivozanib as a first-line treatment for RCC to the European Medicines Agency, or EMA, in February 2016, which is further discussed below, the survival status of additional patients was taken into account and the updated median OS for the tivozanib arm was 28.2 months and the updated median OS for the sorafenib arm was 30.8 months (hazard ratio (HR)=1.147, p=0.276). We believe that an imbalance in subsequent therapy combined with the significant activity seen with tivozanib treatment following sorafenib contributed to the discordance in the efficacy results in the TIVO-1 trial between the PFS and ORR benefit, which significantly favored tivozanib, and the OS, which trended in favor of sorafenib. In 2012, we submitted an NDA to the FDA seeking U.S. marketing approval for tivozanib. In June 2013, the FDA issued a complete response letter informing us that it would not approve tivozanib for the first-line treatment of RCC based solely on the data from this single pivotal trial (TIVO-1), and recommended that we perform an additional clinical trial adequately sized to assure the FDA that tivozanib does not adversely affect 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 RCC received tivozanib as second-line treatment subsequent to disease progression on the sorafenib treatment arm in the TIVO-1 first-line RCC trial. We presented the results at the 2015 American Society of Clinical Oncology, or ASCO, Annual Meeting. In March 2018, long-term follow-up results from Study 902 were published in the European Journal of Cancer under the title "Efficacy of Tivozanib Treatment after Sorafenib in Patients with Advanced Renal Cell Carcinoma: Crossover of a Phase 3 Study," reporting a median PFS of 11.0 months, a median OS of 21.6 months and an 18% ORR, further supporting the rationale for our current phase 3 TIVO-3 trial discussed below.

First-Line Approval in Europe: In February 2016, EUSA submitted an application for the use of tivozanib as a first-line treatment for RCC to the EMA based on the data from our TIVO-1 clinical trial, as supported by data from

the TIVO-1 extension trial, one phase 1 trial and two phase 2 trials in RCC. In June 2017, following an oral explanation, the Committee for Medicinal Products for Human Use, or CHMP, which is the scientific committee of the EMA, issued an opinion recommending tivozanib for approval. In August 2017, the European Commission granted marketing authorization to EUSA for tivozanib in all 28 countries of the EU, Norway and Iceland. Tivozanib is sold under the brand name FOTIVDA, and is approved for the first-line treatment of adult patients with RCC and for adult patients who are VEGFR and mTOR pathway inhibitor-naïve following disease progression after one prior treatment with cytokine therapy for RCC.

EUSA has commercially launched FOTIVDA in the United Kingdom, Germany, Austria, the Netherlands and Sweden. In November 2017, EUSA initiated product sales in Germany and in November 2018, EUSA received reimbursement approval from the German Federal Association of the Statutory Health Insurances, or GKV-SV, for the first-line treatment of adult patients with RCC. In February 2018, EUSA commercially launched FOTIVDA in the United Kingdom upon receiving reimbursement approval from the United Kingdom's National Institute for Health and Care Excellence, or the NICE, for the first-line treatment of adult patients with RCC. EUSA is working to secure reimbursement approval in Italy, Spain and France and commercially launch FOTIVDA in additional European countries. In January 2019, we were informed by EUSA that the CHMP requested the topline data results from our TIVO-3 trial for review at the CHMP's January 2019 plenary meeting under its post-authorization monitoring procedures. Subsequently, EUSA has informed us that the CHMP has requested additional data analysis from our TIVO-3 trial.

In the updated Clinical Practice Guidelines for the diagnosis, treatment and follow-up of RCC by the European Society for Medical Oncology, or ESMO, published in February 2019, tivozanib has been added as a first-line treatment for patients with good or intermediate risk and as a second-line treatment for patients following first-line TKIs.

Third-Line and Fourth-Line Phase 3 Trial (TIVO-3): In May 2016, we initiated enrollment in the TIVO-3 trial, a phase 3 trial of tivozanib in the third- and fourth-line treatment of patients with RCC. The TIVO-3 clinical trial was designed to address the FDA's concern about the negative OS trend expressed in the complete response letter from June 2013. TIVO-3, together with the previously completed TIVO-1 trial of tivozanib in the first-line treatment of RCC, is designed to support a regulatory submission of tivozanib in the United States as a treatment for RCC in multiple lines of therapy. Our TIVO-3 trial design, which we reviewed with the FDA, provides for a randomized, controlled, multi-center, open-label phase 3 clinical trial, with subjects randomized 1:1 to receive either tivozanib or sorafenib. Subjects enrolled in the trial must have failed two systemic therapies, including a VEGFR TKI. Patients may have received prior immunotherapy, including immune checkpoint (PD-1) inhibitors, reflecting the evolving treatment landscape. The primary objective of the TIVO-3 trial is to show improved PFS. Secondary endpoints include OS, safety and ORR. The trial's sites are located in North America and Europe. The TIVO-3 trial does not include a crossover design; accordingly, the protocol does not provide for patients who progress in one therapy to cross over to the other therapy.

The TIVO-3 trial enrolled a total of 350 patients. In October 2017, TIVO-3 successfully passed a pre-planned interim futility analysis. Based on the results of the futility analysis, which were reviewed by an independent statistician, the trial continued as planned without modification. The trial has also passed three semi-annual safety data assessments.

On November 5, 2018, we announced positive topline results for the primary endpoint of the TIVO-3 trial. The trial met its primary endpoint for PFS, with a median PFS in the tivozanib arm of 5.6 months compared with 3.9 months in the sorafenib arm. Tivozanib demonstrated a 44% improvement in median PFS and 26% reduction in risk of progression or death compared to sorafenib (HR=0.74, p=0.02). Approximately 26% of patients received checkpoint inhibitor therapy in earlier lines of treatment, and PFS for tivozanib was longer than for sorafenib both in patients who received prior checkpoint inhibitor therapy and those who received two prior VEGF TKI therapies. Patients who received prior checkpoint inhibitor therapy had a median PFS of 7.3 months with tivozanib and 5.1 months with sorafenib (HR=0.55, p=0.03). The analysis of the secondary endpoint of OS was not mature at the time of the final PFS analysis and after taking into account the survival status of a group of patients that were previously lost to follow-up, the preliminary OS analysis showed a hazard ratio of 1.12 and a p-value of 0.44. The secondary endpoint of ORR for patients receiving tivozanib was 18% compared to 8% for patients receiving sorafenib (p=0.02). Median duration of response in patients receiving tivozanib was not reached and in patients receiving sorafenib was 5.7 months. Tivozanib was generally better tolerated than sorafenib, with Grade 3 or higher adverse events consistent with those observed in previous tivozanib trials. Infrequent but severe adverse events reported in greater number in the tivozanib arm were thrombotic events similar to those observed in previous tivozanib studies. The most common adverse event in patients receiving tivozanib was hypertension, an adverse event known to reflect effective VEGF

pathway inhibition.

At a meeting in January 2019 with the FDA, the FDA recommended that we not submit an NDA for tivozanib at this time as the preliminary OS results from the TIVO-3 trial did not allay its concerns about a potential detriment in OS outlined in its complete response letter delivered to us in June 2013 regarding the TIVO-1 trial, which had shown a protocol-specified final OS hazard ratio of 1.245. On February 5, 2019, we received final minutes from that meeting with the FDA. The minutes reflect our agreement with the FDA not to submit an NDA for tivozanib at this time and include the FDA's recommendation that we not conduct any exploratory OS analyses. We previously planned to conduct the final OS analysis per protocol in August 2019. However, due to the longer-than-expected median OS in both the tivozanib and sorafenib arms, and following our discussion with the FDA, we plan to designate the OS analysis to be conducted in August 2019 as a second interim analysis. We anticipate reporting the results of this analysis in the fourth quarter of 2019, and plan to provide an update regarding the potential submission of an NDA for tivozanib to the FDA.

RCC PD-1 Combination Trial with Opdivo® (TiNivo): In recent clinical trials, VEGFR TKI and immune checkpoint (PD-1) inhibitor combinations have shown promising efficacy in treating RCC. However, several combinations of non-specific VEGFR TKIs with anti-PD-1 antibodies have encountered toxicity levels that we believe have challenged or prohibited such VEGFR TKIs from safely combining with PD-1 inhibitors for RCC treatment, or required them to combine at reduced doses, which can potentially reduce efficacy. In our clinical trials, tivozanib has demonstrated lower rates of key potential overlapping toxicities with PD-1 inhibitors. Based on this data, we believe that tivozanib's tolerability profile may allow tivozanib to combine with PD-1 inhibitors with improved tolerability relative to other TKI plus PD-1 combinations reported to date.

In March 2017, we initiated enrollment in the TiNivo trial, a phase 1b/2 clinical trial of tivozanib in combination with Opdivo (nivolumab), an immune checkpoint (PD-1) inhibitor, for the treatment of RCC. The TiNivo trial enrolled a total of 28 patients. We are sponsoring the trial, for which Bristol-Myers Squibb, or BMS, has supplied nivolumab. 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 1b portion of the TiNivo trial enrolled six patients. In June 2017, we successfully completed the phase 1 dose escalation portion of the trial, where oral tivozanib was administered in two escalating dose cohorts in combination with intravenous nivolumab at a constant 240 mg every two weeks. The full dose tivozanib regimen of 1.5 mg daily for 21 days, followed by a 7-day rest period, was selected as the recommended phase 2 dose for the expansion portion of the trial. On November 3, 2017, the results from the phase 1b portion of the TiNivo trial were presented at the 16th International Kidney Cancer Symposium of the Kidney Cancer Association. The phase 1b portion of the TiNivo trial demonstrated that the combination of tivozanib and nivolumab was well tolerated to the full dose and schedule of single agent tivozanib, with no dose limiting toxicities.

The phase 2 portion of the trial, which enrolled an additional 22 patients, was designed to assess the safety, tolerability, and anti-tumor activity of the combination of tivozanib and nivolumab. On February 10, 2018, we presented preliminary results from the phase 2 portion of the TiNivo trial at the 2018 ASCO Genitourinary Cancers Symposium. On October 22, 2018, we presented updated interim results from all 25 patients treated at full dose at the ESMO 2018 Congress. The combination was generally well tolerated. Treatment-related Grade 3/4 adverse events occurred in 60% of patients, the most common of which was hypertension. Preliminary efficacy was assessed in all 25 patients, who were treated with the full dose and schedule of oral tivozanib in combination with intravenous nivolumab. Of these patients, 13 (52%) had received at least one prior systemic therapy, including two (8%) that had received prior PD-1 therapy, and 12 (48%) were treatment naïve. An ORR was observed in 14 patients (56%) (complete response plus partial response), including one patient (4%) achieving a complete response, and a disease control rate (complete response plus partial response plus stable disease) was observed in 24 patients (96%). Of the two patients (8%) who received prior PD-1 therapy, one achieved a partial response and the other achieved stable disease. At the time of data collection, 13 patients (52%) remained on study and 18 patients (72%) had tumor shrinkage of at least 25%, with a majority of patients having disease control for at least 48 weeks.

Clinical Development in HCC

NCCN-AVEO Phase 1b/2 Trial. In January 2018, Dr. Renuka Iyer from the Roswell Park Cancer Institute presented data at the 2018 ASCO Gastrointestinal Cancers Symposium from a multicenter, investigator-sponsored phase 1b/2 trial of tivozanib in previously untreated patients with advanced, unresectable HCC. The trial was one of several studies funded by a grant we provided to the National Comprehensive Cancer Network.

The trial was designed to evaluate the safety and efficacy of tivozanib in advanced HCC, and enrolled a total of 21 patients at three trial sites. In the phase 1b portion of the trial, which used a modified 3 + 3 dose escalation design, 8 patients were dosed with tivozanib starting at 1.0 mg or 1.5 mg daily for 21 days followed by 7 days off drug. No dose-limiting toxicities were seen in cycle one in patients treated with 1.0 mg, and tivozanib at 1.0 mg daily was selected for the phase 2 expansion portion of the trial.

Of 19 evaluable patients in the trial, at a median follow up of 16.9 months, the trial's primary endpoint of median PFS and PFS at week 24 were 5.5 months and 47%, respectively. A partial response was seen in 4 of 19 patients (21%) and stable disease in 8 of 19 patients (42%), for a disease control rate of 63%. OS at 6 and 12 months was 58% and 25%, respectively, with a median OS of 7.5 months. As of the date of the presentation, four patients had maintained stable disease for over two years. There were no significant changes in hepatitis B or hepatitis C viral load during study treatment. Tivozanib was generally well tolerated at 1.0 mg daily, with adverse events consistent with those observed in previous tivozanib trials.

HCC PD-L1 Combination Trial with IMFINZI®: On December 11, 2018, we entered into a clinical supply agreement with a wholly-owned subsidiary of AstraZeneca PLC, or AstraZeneca, to evaluate the safety and efficacy of AstraZeneca's IMFINZI (durvalumab), a human monoclonal antibody directed against programmed death-ligand 1, or PD-L1, in combination with tivozanib as a first-line treatment for patients with advanced, unresectable HCC in a phase 1/2 study. We will serve as the study sponsor; each party will contribute the clinical supply of its study drug; and study costs will be otherwise shared equally. The phase 1 portion of the study is expected to commence in 2019.

Ficlatuzumab

Ficlatuzumab is a potent HGF inhibitory antibody. HGF is the sole known ligand of the c-Met receptor, which is believed to trigger many activities that are involved in cancer development and metastasis. We have partnered with Biodesix, Inc., or Biodesix, under a worldwide Co-Development and Collaboration Agreement, or the Biodesix Agreement, to develop and commercialize ficlatuzumab. Under the Biodesix Agreement, we and Biodesix each contribute half of the development costs of ficlatuzumab.

Development in HNSCC. We and Biodesix funded an investigator-sponsored phase 1 clinical trial of ficlatuzumab in combination with cetuximab in HNSCC. In June 2017, preliminary results from the phase 1 trial were presented at the 2017 ASCO Annual Meeting. The trial of ficlatuzumab in combination with the EGFR inhibitor cetuximab in patients with cetuximab-resistant, metastatic HNSCC demonstrated activity with an overall response rate of 17% (two partial responses out of twelve patients), a disease control rate of 67% and prolonged PFS and OS compared to historical controls, in addition to being well tolerated. A randomized, phase 2, multicenter, investigator-initiated trial in ERBITUX® (cetuximab) refractory patients to confirm these findings was initiated in the fourth quarter of 2017 under the direction of Julie E. Bauman, MD, MPH, Chief, Division of Hematology/Oncology at the University of Arizona Cancer Center. The phase 2 trial is designed to enroll approximately 60 patients randomized to receive either ficlatuzumab alone or ficlatuzumab and cetuximab.

Development in AML. We and Biodesix are funding an investigator-sponsored phase 1/2 clinical trial of ficlatuzumab in combination with cytarabine in AML. In June 2017, preliminary results from the phase 1 trial were presented at the 2017 ASCO Annual Meeting. This trial, exploring ficlatuzumab in combination with high-dose cytarabine in patients with high risk relapsed or refractory AML, demonstrated early signs of tolerability and activity, including a 50% complete response rate in the eight evaluable patients. The phase 2 portion is ongoing and expected to enroll ten additional patients. On April 1, 2019, data from the phase 1b expansion cohort is scheduled to be presented at the 2019 American Association for Cancer Research Annual Meeting.

Development in pancreatic cancer. We and Biodesix are funding an investigator-sponsored phase 1/2 clinical trial of ficlatuzumab in combination with nab-paclitaxel and gemcitabine in pancreatic cancer. The trial was initiated in December 2017 to test the safety and tolerability of ficlatuzumab when combined with nab-paclitaxel and gemcitabine in previously untreated metastatic pancreatic ductal cancer, or PDAC. Preclinical findings demonstrated a beneficial effect of the drug combination of ficlatuzumab and gemcitabine compared to either drug alone in an in-vivo model of PDAC. The trial is designed to determine maximum tolerated dose of ficlatuzumab when combined with gemcitabine and nab-paclitaxel. Secondary outcome measures include response rate and PFS. The trial, which is being conducted under the direction of Kimberly Perez, M.D. at the Dana-Farber Cancer Institute, is expected to enroll approximately 24 patients.

We continue to evaluate additional opportunities for the further clinical development of ficlatuzumab. The expansion of the ficlatuzumab clinical program, beyond what we are committed to, would require additional manufacturing efforts and costs.

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 (also known as heregulin), or NRG1, levels predict AV-203 anti-tumor activity. We have completed a phase 1 dose escalation trial 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.

We have partnered with CANbridge Life Sciences Ltd., or CANbridge, to develop, manufacture and commercialize AV-203 in all countries outside of North America. We have retained the North American rights to AV-203. CANbridge's obligations include conducting and funding clinical development of AV-203 through phase 2 proof-of-concept in ESCC. Following proof-of-concept, we may decide to participate in later-stage worldwide development efforts. In December 2017, CANbridge filed an IND in China seeking regulatory authorization to initiate clinical trials of AV-203, which CANbridge refers to as CAN017, in ESCC. In August 2018, the China National Drug Administration, or CNDA, approved this IND application. CANbridge has advised us that it plans to initiate a phase 1b/extension trial in ESCC in 2019.

AV-380

AV-380 is a potent humanized IgG1 inhibitory monoclonal antibody targeting 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, anorexia nervosa and other diseases. AV-380 focuses on a significant area of unmet 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 believe that AV-380 represents a unique approach to treating cachexia because it has been demonstrated to address key underlying mechanisms of the syndrome. 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 OS benefit. We have demonstrated preclinical proof-of-concept for AV-380 in multiple cancer cachexia models and have completed cell line development. 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.

In August 2015, we entered into a license agreement pursuant to which we granted Novartis International Pharmaceutical Ltd., or Novartis, the exclusive right to develop and commercialize AV-380 and our related antibodies worldwide. On June 29, 2018, Novartis notified us that it would be terminating the agreement, which we refer to as the Novartis License Agreement, without cause, following a change in strategic direction at Novartis. Effective August 28, 2018, we regained worldwide rights to the AV-380 program, and on December 18, 2018, we entered into a new agreement with Novartis, or the AV-380 Transfer Agreement, to further establish and clarify the terms on which Novartis will return the AV-380 program to us to support our continuing development of the AV-380 program. We are working to initiate preclinical toxicology studies mid-2019 to support a potential IND filing with the FDA.

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, such as pulmonary arterial hypertension, and neurodegenerative conditions. We are currently evaluating options to develop the AV-353 platform.

Competition

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, or of different types of products targeting the same indications we are pursuing. A number of multinational pharmaceutical companies, as well as large biotechnology companies, including, but not limited to, Amgen Inc., ArQule, Inc.,

AstraZeneca, Bayer HealthCare AG, or Bayer, BMS, Eisai Co., Ltd., or Eisai, Eli Lilly and Company, or Lilly, Exelixis, Inc., or Exelixis, Gilead Sciences, Inc., GlaxoSmithKline plc, or GSK, Helsinn Healthcare S.A., or Helsinn, XBiotech Inc., Incyte Corporation, or Incyte, Janssen Pharmaceuticals, Inc. (a division of Johnson and Johnson), Jazz Pharmaceuticals plc, Merck & Co., Inc., or Merck, NGM Biopharmaceuticals, Inc., or NGM Bio, Novartis, Pfizer Inc., or Pfizer, and Roche Laboratories, Inc, or Roche, are pursuing development in diseases we focus on or are currently developing or marketing pharmaceuticals that target VEGFR, HGF/c-Met, ErbB3, GDF15/GFRAL (the receptor to GDF15), Notch 3 or other pathways on which we may focus. 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 pharmaceutical discovery and development, obtaining FDA and other regulatory approvals, and product commercialization. Many are already marketing products to treat the same indications, or having the same biological targets, as the product candidates we are developing, including with respect to RCC. In addition, many of these competitors have significantly greater commercial infrastructures than we have. We will not be able to compete successfully unless and until 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/or 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.

Tivozanib

There are currently 11 FDA-approved drugs in oncology which, like tivozanib, target the VEGFR pathway as a part or all of their inhibitory mechanism. Eight of the FDA-approved VEGF pathway inhibitors are oral small molecule receptor TKIs. Nexavar (sorafenib) and Stivarga (regorafenib) are marketed by Bayer, 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 VEGFR 1, 2 and 3. Nexavar is approved for RCC and unresectable HCC. Stivarga is approved for refractory metastatic colorectal cancer, or mCRC, HCC in patients previously treated with sorafenib, and refractory gastrointestinal stromal tumors, or GIST. Sutent is approved for RCC, GIST, and progressive, well-differentiated pancreatic neuroendocrine tumors. Inlyta is approved for RCC after failure of one prior systemic therapy. Votrient is approved for RCC and advanced soft tissue sarcoma after prior chemotherapy. Caprelsa (vandetanib), marketed by Sanofi Genzyme is approved for advanced medullary thyroid cancer, Lenvima (lenvatinib) marketed by Eisai is approved for differentiated thyroid cancer, RCC following one prior anti-angiogenic therapy in combination with everolimus, and unresectable HCC and Cabometyx (cabozantinib), marketed by Exelixis, is approved for RCC and HCC in patients previously treated with sorafenib.

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 and ovarian cancer, cervical cancer, non-squamous non-small cell lung cancer, and metastatic RCC in combination with interferon alfa. 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 as monotherapy or in combination with paclitaxel, metastatic CRC in combination with FOLFIRI and in combination with docetaxel for the treatment of non-small-cell lung carcinoma, or 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 and other immune system-targeted therapies, both alone and in combination, present additional competition for tivozanib. We are aware of several phase 3 registration studies evaluating PD-1/PD-L1 inhibitors in combination with VEGFR TKIs in RCC, as well as combinations of PD-1 agents with other immune therapies for RCC. The FDA approved the combination of Opdivo and Yervoy for first-line RCC patients with intermediate or poor risk prognosis in April 2018. In addition, the IMmotion151 phase 3 combination study of bevacizumab and atezolizumab versus sunitinib in first-line RCC reported positive results for one of the co-primary endpoints (PFS), the JAVELIN Renal 101 phase 3 combination study of axitinib and avelumab versus sunitinib in first-line RCC reported positive results for one of the co-primary endpoints (PFS in PD-L1+ patients), and the KEYNOTE-426 phase 3 combination study of axitinib and pembrolizumab versus sunitinib in first-line RCC reported positive results for both primary endpoints of PFS and OS. Phase 3 studies for the treatment of HCC have been initiated for the combination of bevacizumab and atezolizumab as well as the combination of lenvatinib and pembrolizumab. If these additional combinations are approved, they could present additional competition for tivozanib.

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 include 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's XL-184 (Cometriq/Cabometyx, cabozantinib), Mirati Therapeutics' glesatinib, Incyte's and Novartis's INCB-028060, Amgen BioPharma's AMG-337, Lilly's merestinib (LY2801653), AstraZeneca and Hutchison MediPharma Limited's savolitinib, Merck KGaA's tepotinib, AbbVie Inc.'s ABBV-299, and Betta Pharmaceuticals Co., Ltd.'s BPI-9016.

AV-203

We believe the most direct competitors to our AV-203 program are monoclonal antibodies that specifically target the ErbB3 receptor, including Daiichi Sankyo, Inc.'s and Amgen Inc.'s patritumab (AMG-888), which has ongoing phase 2 clinical development for metastatic breast cancer. Other clinical-stage ErbB3-specific competitors include Merus N.V.'s MCLA-128, AstraZeneca's sapitinib, Celldex Therapeutics Inc.'s CDX-3379, and Sihuan Pharmaceutical Holdings Group Ltd.'s pirotinib. Clinical stage competitors targeting ErbB3 in addition to other targets include Roche's duligotuzumab. Merrimack Pharmaceuticals recently announced termination of the MM-121 programs in NSCLC and metastatic breast cancer based on futility of results from the phase 2 NSCLC study.

AV-380

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.

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) and Ohr Pharmaceutical, Inc.'s OHR118 (cytoprotectant/immunomodulator). NGM Bio is currently running a phase 1 trial of NGM120 (an antagonistic antibody to GFRAL).

AV-353 Platform

There are currently no Notch 3-specific inhibitors approved or in clinical trials in oncology. 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 and Tarextumab (OMP-59R5), which failed to show benefit in a phase 2 small cell lung cancer study.

Strategic Partnerships

We have established various strategic partnerships with leading pharmaceutical companies for our product candidates and programs in our portfolio. Under each of our strategic partnerships, we are entitled to receive or required to pay upfront, milestone payments and/or royalties. For information on our collaboration agreements focused solely on the clinical development of tivozanib in combination with immune checkpoint inhibitors, see "— Our Product Candidates — Tivozanib — Clinical and Regulatory Development in RCC — RCC PD-1 Combination Trial with Opdivo (TiNivo)" and "— Our Product Candidates — Tivozanib — Clinical Development in HCC — HCC PD-L1 Combination Trial with IMFINZI."

CANbridge

In March 2016, 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 all countries outside of North America. In addition, CANbridge has a right of first negotiation if we determine to outlicense any North American rights. The parties have both agreed not to develop or commercialize any ErbB3 inhibitory antibody other than AV-203 during the term of the CANbridge Agreement. CANbridge has responsibility for all activities and costs associated with the development, manufacture and commercialization of AV-203 in its territories. 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. Under the CANbridge Agreement, CANbridge is required to conduct and fund the clinical development of AV-203 through phase 2 proof-of-concept in esophageal squamous cell carcinoma, or ESCC, after which we may elect to contribute to certain worldwide development efforts.

In December 2017, CANbridge filed an IND application with the CNDA for a clinical study of AV-203 in ESCC. CANbridge's IND application was accepted by the CNDA in August 2018. CANbridge has advised us that it plans to initiate a phase 1b/extension trial in ESCC in 2019.

Upon entry into the CANbridge Agreement, CANbridge paid us an upfront fee of $1.0 million in April 2016, net of foreign withholding taxes. CANbridge also reimbursed us for $1.0 million in certain AV-203 manufacturing costs that we previously incurred. CANbridge paid this manufacturing reimbursement in two installments of $0.5 million each, one in March 2017 and one in September 2017, net of foreign withholding taxes. In August 2018, CANbridge obtained regulatory approval of its IND application from the CNDA for a clinical study of AV-203 in ESCC and, accordingly, we earned a $2.0 million development and regulatory milestone payment that was received from CANbridge in August 2018.

Pursuant to the CANbridge Agreement, we are eligible to receive up to $40.0 million in potential additional development and regulatory milestone payments and up to $90.0 million in potential commercial 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 or 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 under the CANbridge Agreement, excluding upfront and reimbursement payments, are due to Biogen Idec International GmbH, or Biogen, as a sublicensing fee under our option and license agreement with Biogen dated March 18, 2009, as amended. The $2.0 million development and regulatory milestone we earned in August 2018 for regulatory approval from the CNDA of an IND application for a clinical study of AV-203 in ESCC was subject to this sublicense fee, or $0.7 million, which was paid to Biogen in October 2018.

The term of the CANbridge Agreement continues 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, or the EUSA Agreement, 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 and Australasia for all diseases and conditions in humans, excluding non-oncologic ocular conditions. EUSA is obligated to use commercially reasonable efforts to seek regulatory approval for and commercialize tivozanib throughout its licensed territories for RCC. EUSA has responsibility for all activities and costs associated with the further development, manufacture, regulatory filings and commercialization of tivozanib in its licensed territories.

EUSA made research and development reimbursement payments to us of $2.5 million upon the execution of the EUSA Agreement in 2015, and $4.0 million in September 2017 upon its receipt of marketing authorization from the European Commission in August 2017 for tivozanib (FOTIVDA) for the treatment of RCC. In September 2017, EUSA elected to opt-in to co-develop the TiNivo trial. As a result of EUSA's exercise of its opt-in right, it became an active participant in the ongoing conduct of the TiNivo trial and is able to utilize the resulting data from the TiNivo trial for regulatory and commercial purposes in its territories. EUSA made an additional research and development reimbursement payment to us of $2.0 million upon its exercise of its opt-in right. This payment was received in October 2017, in advance of the completion of the TiNivo trial, and represents EUSA's approximate 50% share of the total estimated costs of the TiNivo trial. We are also eligible to receive an additional research and development reimbursement payment from EUSA of 50% of our total costs for our TIVO-3 trial, up to $20.0 million, if EUSA elects to opt-in to that study.

We are 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, which we refer to collectively as the EU5, and an additional $2.0 million for the grant of marketing approval for RCC, if any, in three of the licensed countries outside of the EU, as mutually agreed by the parties. In February 2018 and in November 2018, EUSA obtained reimbursement approval from the NICE in the United Kingdom and the GKV-SV in Germany, respectively, for the first-line treatment of RCC. Accordingly, we earned a $2.0 million milestone payment with respect to the reimbursement approval in the United Kingdom that was received from EUSA in March 2018 and a $2.0 million milestone payment with respect to the reimbursement approval in Germany that was received from EUSA in December 2018. We are also eligible to receive a payment of $2.0 million per indication 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. Upon commercialization, we are 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. In November 2017, we began earning sales royalties upon EUSA's commencement of the first commercial launch of tivozanib (FOTIVDA) with the initiation of product sales in Germany. The commercial launch expanded to the United Kingdom following the reimbursement approval by the NICE in February 2018. In addition, EUSA has launched FOTIVDA in several non-EU5 European countries and is working toward launching FOTIVDA in additional European territories. We recognized approximately $0.5 million and $19,000 in revenue for sales royalties in the years ended December 31, 2018 and 2017, respectively.

The research and development reimbursement payments under the EUSA Agreement are not subject to the 30% sublicensing payment payable to KHK, subject to certain limitations. We would, however, owe KHK 30% of other, non-research and development payments we may receive from EUSA pursuant to the EUSA Agreement, including any reimbursement approvals for RCC in the EU5, marketing approvals for RCC in three specified non-EU licensed territories, EU marketing approval filings and corresponding marketing approvals by the EMA for up to three additional indications beyond RCC, and sales-based milestones and royalties, as set forth above. The $2.0 million milestone payments we earned in each of February 2018 and November 2018 upon EUSA's reimbursement approval for FOTIVDA in the United Kingdom and in Germany, respectively, were subject to the 30% KHK sublicense fee, or $0.6 million, each. We paid the sublicense fees for EUSA's reimbursement approvals in the United Kingdom and Germany in April 2018 and in January 2019, respectively.

The term of the EUSA Agreement continues 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 tenth anniversary of the effective date. Either party may terminate the EUSA 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 EUSA Agreement, and (b) ninety (90) days in the case of any other material breach. EUSA may terminate the EUSA Agreement at any time upon one hundred eighty

(180) days' prior written notice. In addition, we may terminate the EUSA Agreement upon thirty (30) days' prior written notice if EUSA challenges any of the patent rights licensed under the EUSA Agreement.

Novartis

In August 2015, we entered into the Novartis License Agreement, under which we granted Novartis the exclusive right to develop and commercialize AV-380 and our related antibodies worldwide. Novartis was responsible under the Novartis License Agreement for the development, manufacture and commercialization of our antibodies and any resulting approved therapeutic products. On June 29, 2018, Novartis notified us that it would be terminating our collaboration without cause following a change in strategic direction at Novartis. Effective August 28, 2018, the Novartis License Agreement was terminated and we regained worldwide rights to the AV-380 program. Novartis' termination without cause triggered the termination of all licenses and other rights granted by us to Novartis with regard to the AV-380 program, and the grant by Novartis to us of an irrevocable, exclusive, fully paid-up license, with a right to sub-license, to any patent rights or know-how controlled by Novartis as of the termination date related to the AV-380 program. Following termination, Novartis has initiated the process of transferring the AV-380 program back to us.

On December 18, 2018, we entered into the AV-380 Transfer Agreement to further establish and clarify the terms on which the AV-380 program will be returned to us, and to support our continuing development of the AV-380 program. The AV-380 Transfer Agreement provides for the continued transfer to AVEO of all preclinical, technical, manufacturing and other data developed by Novartis relating to the AV-380 program, as well as cooperation regarding our future regulatory filings relating to AV-380. Pursuant to the AV-380 Transfer Agreement, Novartis also agreed to provide the AV-380 drug supply, valued at approximately $4.0 million, to us at no charge, and to make a one-time payment to us of $2.3 million, which was paid to us in January 2019 and we used to cover the $2.3 million time-based milestone obligation due to St. Vincent's in January 2019 under our license agreement as further described below under the heading "—St. Vincent's Hospital." The AV-380 Transfer Agreement contains mutual releases by both parties of all claims arising out of the Novartis License Agreement, other than indemnification obligations. Novartis has also agreed that it will not develop, manufacture or commercialize any anti-GDF15 antagonist antibody for three years following the date of the AV-380 Transfer Agreement.

Biodesix

In April 2014, we entered into a worldwide co-development and collaboration agreement with Biodesix, or the Biodesix Agreement, to develop and commercialize ficlatuzumab. Under the Biodesix Agreement, we and Biodesix are each required to contribute 50% of all clinical, regulatory, manufacturing and other costs to develop ficlatuzumab, and would share equally in any future revenue from development or commercialization, subject to certain exceptions. We retain primary responsibility for clinical development of ficlatuzumab, although all trials are conducted pursuant to a joint development plan.

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. In October 2016, we amended the Biodesix agreement in connection with 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.

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 Biodesix Agreement remains in effect until the expiration of all payment obligations between the parties related to development and commercialization of ficlatuzumab, unless earlier terminated.

We and Biodesix are currently funding several investigator-sponsored clinical trials, including ficlatuzumab in combination with ERBITUX® (cetuximab) in squamous cell carcinoma of the head and neck, ficlatuzumab in combination with Cytosar (cytarabine) in acute myeloid leukemia and ficlatuzumab in combination with nab-paclitaxel and gemcitabine in pancreatic cancer. We continue to evaluate additional opportunities for the further clinical development of ficlatuzumab. Such clinical development, beyond what we are committed to, would require

additional manufacturing efforts and costs.

St. Vincent's Hospital

In July 2012, we entered into a license agreement with St. Vincent's, or the St. Vincent's Agreement, under which we obtained an exclusive, worldwide sublicensable right to 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 St. Vincent's Agreement, we have non-exclusive rights to certain related diagnostic products and research tools and also 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. We are obligated to use diligent efforts to conduct research and clinical development and commercially launch at least one licensed therapeutic product.

In 2012, we paid St. Vincent's an upfront license fee of $0.7 million. In August 2015, in connection with the execution of the Novartis Agreement, we amended and restated the St. Vincent's Agreement and paid St. Vincent's an additional upfront fee of $1.5 million. We are required to make future milestone payments, up to an aggregate total of $14.4 million (exclusive of the $2.3 million milestone payment due in January 2019 described below), 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, depending on the sublicensed territory. In February 2017, Novartis agreed to pay $1.8 million out of its then future payment obligations to us under the former Novartis Agreement. These funds were used to satisfy a $1.8 million time-based milestone obligation that we owed to St. Vincent's in March 2017. As further described above under the heading "—Novartis", we used the $2.3 million payment received from Novartis in January 2019, pursuant to the AV-380 Transfer Agreement, to cover a $2.3 million time-based milestone obligation that became due to St. Vincent's in January 2019. In addition, we will be required to pay St. Vincent's tiered royalty payments equal to a low-single-digit percentage of any net sales we or our sublicensees make from licensed therapeutic products. The royalty rate escalates within the low-single-digit range during each calendar year based on increasing licensed therapeutic product sales during such calendar year. Our royalty payment obligations for a licensed therapeutic product in a particular country end on the later of 10 years after the date of first commercial sale of such licensed therapeutic product in such country or expiration of the last-to-expire valid claim of the licensed patents covering such licensed therapeutic product in such country and are subject to offsets under certain circumstances.

The St. Vincent's Agreement remains 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 St. Vincent's Agreement earlier. We have the right to terminate the St. Vincent's 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 preclinical 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 St. Vincent's Agreement.

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 CANbridge Agreement. 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 of AV-203, up to a cumulative maximum amount of $50.0 million.

The $2.0 million development and regulatory milestone we earned in August 2018 in connection with CANbridge's regulatory approval from the CNDA of an IND application for a clinical study of AV-203 in ESCC was subject to this sublicense fee, or $0.7 million, which was paid to Biogen in October 2018.

Kyowa Hakko Kirin

In December 2006, we entered into a license agreement with KHK, or the KHK Agreement, 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 in all potential indications. 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 KHK 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 KHK Agreement.

Under the KHK Agreement, we are obligated to use commercially reasonable efforts to develop and commercialize tivozanib in our territory. 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 payable to KHK under our KHK Agreement. Upon entering into the KHK Agreement, 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 TIVO-1, our first phase 3 clinical trial of tivozanib. In December 2012, we made a $12.0 million milestone payment to KHK in connection with the acceptance by the FDA of our 2012 NDA filing for tivozanib. Each milestone under the KHK Agreement is a one-time only payment obligation. Accordingly, we would not owe a milestone payment to KHK if we file an NDA with the FDA following the availability of more mature OS results. If we obtain approval for tivozanib in the United States, 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 the EUSA Agreement, the sublicense defines the payment obligations of the sublicensee, which may vary from the milestone and royalty payment obligations under our KHK Agreement 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 reimbursement payments or equity investments, subject to certain limitations.

Certain research and development reimbursement payments by EUSA, including the $2.5 million upfront payment in December 2015, the $4.0 million payment in September 2017 upon the receipt of marketing authorization from the European Commission for tivozanib (FOTIVDA) and the $2.0 million payment upon EUSA’s election in September 2017 to opt-in to co-develop the TiNivo trial were not subject to sublicense revenue payments to KHK. In addition, if EUSA elects to opt-in to the TIVO-3 trial, the additional research and development reimbursement payment from EUSA of 50% of the total trial costs, up to $20.0 million, would also not be subject to a sublicense revenue payment to KHK, subject to certain limitations. We would, however, owe KHK 30% of other, non-research and development payments we may receive from EUSA pursuant to the EUSA Agreement, including reimbursement approvals for RCC in up to five specified EU countries, marketing approvals for RCC in three specified non-EU licensed territories, EU marketing approval filings and corresponding marketing approvals by the EMA for up to three additional indications beyond RCC, and sales-based milestones and royalties. The $2.0 million milestone payments we earned in each of February 2018 and November 2018 upon EUSA’s reimbursement approval for FOTIVDA in the United Kingdom and in Germany, respectively, were subject to the 30% KHK sublicense fee, or $0.6 million each. We paid the sublicense fees for EUSA’s reimbursement approvals in the United Kingdom and Germany in April 2018 and in January 2019, respectively.

We are also required to pay tiered royalty payments on net sales we make of tivozanib in our North American 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 KHK 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 KHK Agreement earlier. If we fail to meet our obligations under the KHK Agreement and are unable to cure such failure within specified time periods, KHK can terminate the KHK 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.: 2 granted patents with expirations ranging from 2022 to 2023
- Europe: 2 granted patents with expirations ranging from 2022 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. In addition, Supplementary Protection Certificates, or SPCs, have been granted in Germany, Italy, Portugal, Spain and Sweden, and are pending in 9 additional European countries, including Belgium, Denmark, France, Great Britain, and the Netherlands, for the corresponding patents in those countries that cover the tivozanib molecule, which, if granted, could extend the term of the patent in each of those countries up to 2027.

KHK has filed an International (PCT) patent application directed 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.

Additionally, we have filed a provisional patent application directed to our clinical protocol for using tivozanib to treat refractory cancers, particularly, following therapy with checkpoint inhibitors. If granted, this patent application would expire in 2039.

Ficlatuzumab

With respect to our anti-HGF platform, including ficlatuzumab, we have six 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.: 6 granted patents with expirations ranging from 2027 to 2028
- Europe: 1 granted patent expiring in 2027
- Japan: 2 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 four U.S. patents and two pending U.S. patent applications covering our anti-ErbB3 antibodies, nucleic acids and expression vectors encoding the antibodies, host cells, methods of making the antibodies, and methods of treatment using our anti-ErbB3 antibodies, which are expected to expire from 2031 to 2032. With respect to our anti-ErbB3 platform we have:

- U.S.: 4 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: 2 granted patents, and 2 pending patent applications, 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 granted patents and 1 pending patent application, if granted, with expirations ranging from 2031 to 2032

18

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, and 1 pending patent application, if granted, expiring in 2025
- Japan: 2 granted patents expiring in 2025
- Canada: 1 granted patent expiring in 2025
- Australia: 1 granted patent expiring in 2025

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

With respect to our GDF15 platform, we have:

- U.S.: 2 granted patents, and 4 pending patent applications, if granted, with expirations ranging from 2033 to 2035
- Europe: 4 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: 1 granted patent expiring in 2033, and 1 pending patent application expiring, if granted, in 2035

AV-353 Platform

With respect to our AV-353 platform, we own an issued U.S. patent, a non-provisional U.S. patent application, and an International (PCT) patent application 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 issued U.S. patent and non-provisional U.S. patent application, if granted, would be expected to expire in 2033, whereas the International (PCT) patent application, if nationalized in the United States and granted, would be expected to expire in 2037.

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

- U.S.: 1 granted patent expiring in 2033, and 2 pending patent applications expiring, if granted, ranging from 2033 to 2037
- Europe: 1 allowed patent expiring in 2033 and 1 pending patent application expiring, if granted, in 2037

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. For example, SPCs have been granted in Germany, Italy, Portugal, Spain and Sweden, and are pending in 9 additional European countries, including Belgium, Denmark, France, Great Britain, and the Netherlands, for the corresponding patents in those countries that cover the tivozanib molecule, which, if granted, could extend the term of the patent in each of those countries up to 2027.

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 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 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. 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 United States 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 over 20 other jurisdictions, and for which we have filed applications in additional countries. We own U.S. and EU registrations for a logo containing FOTIVDA in combination with a flame design. We own U.S. registrations for AVEO and AVEO (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, or CMOs.

One of our CMOs has manufactured what we believe to be sufficient quantities of tivozanib drug product (capsules) to support our ongoing and planned clinical trials and potential commercial launch. We currently engage the same CMO to package, label and distribute clinical supplies of tivozanib on an as–needed basis. We also engaged another packager to bottle, label and serialize potential commercial launch supply.

To date, third-party manufacturers have met the needs for manufacturing clinical trial supplies for all our pipeline products. There are alternate manufacturers with capability to supply for current clinical or potential future commercial needs. Contracting with additional CMOs may require significant lead-times and result in 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 EU, extensively regulate, among other things, the research, development, testing, manufacture, quality control, approval, packaging, storage, recordkeeping, labeling, advertising, promotion, distribution, marketing, sales, pricing, reimbursement, 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. The failure of an applicant to comply with the applicable regulatory requirements at any time during the product development process, including non-clinical testing, clinical testing, the approval process or post-approval process, may result in delays to the conduct of a study, regulatory review and approval and/or administrative or judicial sanctions. These sanctions may include, but are not limited to, the FDA's refusal to allow an applicant to proceed with clinical trials, refusal to approve pending applications, license suspension or revocation, withdrawal of an approval, warning letters, adverse publicity, product recalls, product seizures, total or partial suspension of production or distribution, injunctions, fines and civil or criminal investigations and penalties brought by the FDA or Department of Justice, or DOJ, or other government entities, including state agencies.

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;
- 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 GCPs, 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 similar foreign standards, which we refer to as cGMPs, 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.

Following commencement of a clinical trial under an IND, the FDA may also place a clinical hold or partial clinical hold on that trial. Clinical holds are imposed by the FDA whenever there is concern for patient safety and may be a result of new data, findings, or developments in clinical, nonclinical, and/or chemistry, manufacturing, and controls (CMC). A clinical hold is an order issued by the FDA to the sponsor to delay a proposed clinical investigation or to suspend an ongoing investigation. A partial clinical hold is a delay or suspension of only part of the clinical work requested under the IND. For example, a specific protocol or part of a protocol is not allowed to proceed, while other protocols may do so. No more than 30 days after imposition of a clinical hold or partial clinical hold, the FDA will provide the sponsor a written explanation of the basis for the hold. Following issuance of a clinical hold or partial clinical hold, an investigation may only resume after the FDA has notified the sponsor that the investigation may proceed. The FDA will base that determination on information provided by the sponsor correcting the deficiencies previously cited or otherwise satisfying the FDA that the investigation can proceed.

A sponsor may choose, but is not required, to conduct a foreign clinical study under an IND. When a foreign clinical study is conducted under an IND, all FDA IND requirements must be met unless waived. When a foreign clinical

study is not conducted under an IND, the sponsor must ensure that the study complies with certain regulatory requirements of the FDA in order to use the study as support for an IND or application for marketing approval. Specifically, on April 28, 2008, the FDA amended its regulations governing the acceptance of foreign clinical studies not conducted under an investigational new drug application as support for an IND or a new drug application. The final rule provides that such studies must be conducted in accordance with GCP, including review and approval by an independent ethics committee, or IEC, and informed consent from subjects. The GCP requirements in the final rule encompass both ethical and data integrity standards for clinical studies. The FDA's regulations are intended to help ensure the protection of human subjects enrolled in non-IND foreign clinical studies, as well as the quality and integrity of the resulting data. They further help ensure that non-IND foreign studies are conducted in a manner comparable to that required for IND studies.

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. 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 DSMB, 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.

Information about clinical trials must be submitted within specific timeframes to the National Institutes of Health, or NIH, for public dissemination on its ClinicalTrials.gov website.

Expanded Access to an Investigational Drug for Treatment Use

Expanded access, sometimes called "compassionate use," is the use of investigational new drug products outside of clinical trials to treat patients with serious or immediately life-threatening diseases or conditions when there are no comparable or satisfactory alternative treatment options. The rules and regulations related to expanded access are intended to improve access to investigational drugs for patients who may benefit from investigational therapies. FDA regulations allow access to investigational drugs under an IND by the company or the treating physician for treatment purposes on a case-by-case basis for: individual patients (single-patient IND applications for treatment in emergency settings and non-emergency settings); intermediate-size patient populations; and larger populations for use of the drug under a treatment protocol or Treatment IND Application.

When considering an IND application for expanded access to an investigational product with the purpose of treating a patient or a group of patients, the sponsor and treating physicians or investigators will determine suitability when all of the following criteria apply: patient(s) have a serious or immediately life-threatening disease or condition, and there is no comparable or satisfactory alternative therapy to diagnose, monitor, or treat the disease or condition; the potential patient benefit justifies the potential risks of the treatment and the potential risks are not unreasonable in the context or condition to be treated; and the expanded use of the investigational drug for the requested treatment will not interfere initiation, conduct, or completion of clinical investigations that could support marketing approval of the product or otherwise compromise the potential development of the product.

On December 13, 2016, the 21st Century Cures Act, or the Cures Act, established (and the 2017 Food and Drug Administration Reauthorization Act later amended) a requirement that sponsors of one or more investigational drugs for the treatment of a serious disease(s) or condition(s) make publicly available their policy for evaluating and responding to requests for expanded access for individual patients. Although these requirements were rolled out over time, they have now come into full effect. This provision requires drug and biologic companies to make publicly available their policies for expanded access for individual patient access to products intended for serious diseases. Sponsors are required to make such policies publicly available upon the earlier of initiation of a phase 2 or phase 3 study; or 15 days after the drug or biologic receives designation as a breakthrough therapy, fast track product, or

regenerative medicine advanced therapy.

In addition, on May 30, 2018, the Right to Try Act was signed into law. The law, among other things, provides a federal framework for certain patients to access certain investigational new drug products that have completed a phase 1 clinical trial and that are undergoing investigation for FDA approval. Under certain circumstances, eligible patients can seek treatment without enrolling in clinical trials and without obtaining FDA permission under the FDA expanded access program. There is no obligation for a drug manufacturer to make its drug products available to eligible patients as a result of the Right to Try Act, but the manufacturer must develop an internal policy and respond to patient requests according to that policy.

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. Phase 1, phase 2 and phase 3 clinical trials may not be completed successfully within any specified period, or at all. Furthermore, 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.

Concurrent with clinical trials, companies often complete additional animal studies and must also develop additional information about the chemistry and physical characteristics of the drug as well as finalize a process for manufacturing the product in commercial quantities in accordance with cGMP requirements. The manufacturing process must be capable of consistently producing quality batches of the drug candidate and, among other things, must develop methods for testing the identity, strength, quality, purity, and potency of the final drug. Additionally, appropriate packaging must be selected and tested and stability studies must be conducted to demonstrate that the drug candidate does not undergo unacceptable deterioration over its shelf life.

Finally, under the Pediatric Research Equity Act of 2003, an application or supplement thereto must contain data that are adequate to assess the safety and effectiveness of the product for the claimed indications in all relevant pediatric

subpopulations, and to support dosing and administration for each pediatric subpopulation for which the product is safe and effective. Sponsors must also submit pediatric study plans prior to the assessment data. Those plans must contain an outline of the proposed pediatric study or studies the applicant plans to conduct, including study objectives and design, any deferral or waiver requests and other information required by regulation. The applicant, the FDA, and the FDA's internal review committee must then review the information submitted, consult with each other and agree upon a final plan. The FDA or the applicant may request an amendment to the plan at any time.

For drugs intended to treat a serious or life-threatening disease or condition, the FDA must, upon the request of an applicant, meet to discuss preparation of the initial pediatric study plan or to discuss deferral or waiver of pediatric assessments. In addition, FDA will meet early in the development process to discuss pediatric study plans with sponsors and FDA must meet with sponsors by no later than the end-of-phase 1 meeting for serious or life-threatening diseases and by no later than ninety days after FDA's receipt of the study plan. The FDA may, on its own initiative or at the request of the applicant, grant deferrals for submission of some or all pediatric data until after approval of the product for use in adults, or full or partial waivers from the pediatric data requirements. Additional requirements and procedures relating to deferral requests and requests for extension of deferrals are contained in the Food and Drug Administration Safety and Innovation Act, or FDASIA. Unless otherwise required by regulation, the pediatric data requirements do not apply to products with orphan designation.

The FDA Reauthorization Act of 2017 established new requirements to govern certain molecularly targeted cancer indications. Any company that submits an NDA three years after the date of enactment of that statute must submit pediatric assessments with the NDA if the drug is intended for the treatment of an adult cancer and is directed at a molecular target that FDA determines to be substantially relevant to the growth or progression of a pediatric cancer. The investigation must be designed to yield clinically meaningful pediatric study data regarding the dosing, safety and preliminary efficacy to inform pediatric labeling for the product.

Submission and 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 is a vehicle 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 drug product candidate must be the subject of an approved NDA before it may be commercialized in the United States. Under federal law, the submission of most NDAs is subject to an application user fee, which for federal fiscal year 2019 is $2,588,478 for an application requiring clinical data. The sponsor of an approved NDA is also subject to an annual program fee, which for fiscal year 2019 is $309,915. Certain exceptions and waivers are available for some of these fees, such as an exception from the application fee for products with orphan designation and a waiver for certain small businesses.

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. Under the FDA Reauthorization Act of 2017, the FDA must implement a protocol to expedite review of responses to inspection reports pertaining to certain applications, including applications for products in shortage or those for which approval is dependent on remediation of conditions identified in the inspection report.

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 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.

Accelerated Approval Pathway

The FDA may grant accelerated approval to a product for a serious or life threatening condition that provides meaningful therapeutic advantage to patients over existing treatments based upon a determination that the product has an effect on a surrogate endpoint that is reasonably likely to predict clinical benefit. The FDA may also grant accelerated approval for such a condition when the product has an effect on an intermediate clinical endpoint that can be measured earlier than an effect on irreversible morbidity or mortality, or IMM, and that is reasonably likely to predict an effect on irreversible morbidity or mortality or other clinical benefit, taking into account the severity, rarity or prevalence of the condition and the availability or lack of alternative treatments. Products granted accelerated approval must meet the same statutory standards for safety and effectiveness as those granted traditional approval.

For the purposes of accelerated approval, a surrogate endpoint is a marker, such as a laboratory measurement, radiographic image, physical sign or other measure that is thought to predict clinical benefit, but is not itself a measure of clinical benefit. Surrogate endpoints can often be measured more easily or more rapidly than clinical endpoints. An intermediate clinical endpoint is a measurement of a therapeutic effect that is considered reasonably likely to predict the clinical benefit of a drug, such as an effect on IMM. The FDA has limited experience with accelerated approvals based on intermediate clinical endpoints, but has indicated that such endpoints generally may support accelerated approval where the therapeutic effect measured by the endpoint is not itself a clinical benefit and basis for traditional approval, if there is a basis for concluding that the therapeutic effect is reasonably likely to predict the ultimate clinical benefit of a product.

The accelerated approval pathway is most often used in settings in which the course of a disease is long and an extended period of time is required to measure the intended clinical benefit of a product, even if the effect on the surrogate or intermediate clinical endpoint occurs rapidly. Thus, accelerated approval has been used extensively in the

development and approval of products for treatment of a variety of cancers in which the goal of therapy is generally to improve survival or decrease morbidity and the duration of the typical disease course requires lengthy and sometimes large trials to demonstrate a clinical or survival benefit. Thus, the benefit of accelerated approval derives from the potential to receive approval based on surrogate endpoints sooner than possible for trials with clinical or survival endpoints, rather than deriving from any explicit shortening of the FDA approval timeline, as is the case with priority review.

The accelerated approval pathway is usually contingent on a sponsor's agreement to conduct, in a diligent manner, additional post approval confirmatory studies to verify and describe the product's clinical benefit. As a result, a product candidate approved on this basis is subject to rigorous post marketing compliance requirements, including the completion of phase 4 or post approval clinical trials to confirm the effect on the clinical endpoint. Failure to conduct required post approval studies, or confirm a clinical benefit during post marketing studies, would allow the FDA to initiate expedited proceedings to withdraw approval of the product. All promotional materials for product candidates approved under accelerated regulations are subject to prior review by the FDA.

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. If a company is found to have promoted off-label uses, it may become subject to adverse public relations and administrative and judicial enforcement by the FDA, the Department of Justice, or the Office of the Inspector General of the Department of Health and Human Services, as well as state authorities. This could subject a company to a range of penalties that could have a significant commercial impact, including civil and criminal fines and agreements that materially restrict the manner in which a company promotes or distributes drug products.

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.

28

Generic Drugs

In 1984, with passage of the Hatch-Waxman Amendments to the FDCA, 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.

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. This three-year exclusivity period often protects changes to a previously approved drug product, such as a new dosage form, route of administration, combination or indication. Three-year exclusivity would be available for a drug product that contains a previously approved active moiety, provided the statutory requirement for a new clinical investigation is satisfied. Unlike five-year NCE exclusivity, an award of three-year exclusivity does not block the FDA from accepting ANDAs seeking approval for generic versions of the drug as of the date of approval of the original drug product. The FDA typically makes decisions about awards of data exclusivity shortly before a product is approved.

The FDA must establish a priority review track for certain generic drugs, requiring the FDA to review a drug application within eight (8) months for a drug that has three (3) or fewer approved drugs listed in the Orange Book and is no longer protected by any patent or regulatory exclusivities, or is on the FDA's drug shortage list. The new

legislation also authorizes FDA to expedite review of ‘‘competitor generic therapies’’ or drugs with inadequate generic competition, including holding meetings with or providing advice to the drug sponsor prior to submission of the application.

Hatch-Waxman Patent Certification and the 30-Month Stay

Upon approval of an NDA or a supplement thereto, NDA sponsors are required to list with the FDA each patent with claims that cover the applicant’s product or an approved method of using the product. Each of the patents listed by the NDA sponsor is published in the Orange Book. When an ANDA applicant files its application with the FDA, the applicant is required to certify to the FDA concerning any patents listed for the reference product in the Orange Book, except for patents covering methods of use for which the ANDA applicant is not seeking approval. To the extent that the Section 505(b)(2) applicant is relying on studies conducted for an already approved product, the applicant is required to certify to the FDA concerning any patents listed for the approved product in the Orange Book to the same extent that an ANDA applicant would.

Specifically, the applicant must certify with respect to each patent that:

- the required patent information has not been filed;
- the listed patent has expired;
- the listed patent has not expired, but will expire on a particular date and approval is sought after patent expiration; or
- the listed patent is invalid, unenforceable or will not be infringed by the new product.

A certification that the new product will not infringe the already approved product's listed patents or that such patents are invalid or unenforceable is called a Paragraph IV certification. If the applicant does not challenge the listed patents or indicates that it is not seeking approval of a patented method of use, the application will not be approved until all the listed patents claiming the referenced product have expired (other than method of use patents involving indications for which the applicant is not seeking approval).

If the ANDA applicant has provided a Paragraph IV certification to the FDA, the applicant must also send notice of the Paragraph IV certification to the NDA and patent holders once the ANDA has been accepted for filing by the FDA. The NDA and patent holders may then initiate a patent infringement lawsuit in response to the notice of the Paragraph IV certification. The filing of a patent infringement lawsuit within 45 days after the receipt of a Paragraph IV certification automatically prevents the FDA from approving the ANDA until the earlier of 30 months after the receipt of the Paragraph IV notice, expiration of the patent, or a decision in the infringement case that is favorable to the ANDA applicant.

To the extent that the Section 505(b)(2) applicant is relying on studies conducted for an already approved product, the applicant is required to certify to the FDA concerning any patents listed for the approved product in the Orange Book to the same extent that an ANDA applicant would. As a result, approval of a Section 505(b)(2) NDA can be stalled until all the listed patents claiming the referenced product have expired, until any non-patent exclusivity, such as exclusivity for obtaining approval of a new chemical entity, listed in the Orange Book for the referenced product has expired, and, in the case of a Paragraph IV certification and subsequent patent infringement suit, until the earlier of 30 months, settlement of the lawsuit or a decision in the infringement case that is favorable to the Section 505(b)(2) applicant.

Patent Term Restoration and Extension

A patent claiming a new drug product may be eligible for a limited patent term extension under the Hatch-Waxman Act, which permits a patent restoration of up to five years for patent term lost during product development and the FDA regulatory review. The restoration period granted on a patent covering a product is typically one-half the time between the effective date of a clinical investigation involving human beings is begun and the submission date of an application, plus the time between the submission date of an application and the ultimate approval date. Patent term restoration cannot be used to extend the remaining term of a patent past a total of 14 years from the product's approval date. Only one patent applicable to an approved product is eligible for the extension, and the application for the extension must be submitted prior to the expiration of the patent in question. A patent that covers multiple products for which approval is sought can only be extended in connection with one of the approvals. The United States Patent and Trademark Office reviews and approves the application for any patent term extension or restoration in consultation with the FDA.

Biosimilars

The 2010 Patient Protection and Affordable Care Act, or ACA, which was signed into law on March 23, 2010, included a subtitle called the Biologics Price Competition and Innovation Act of 2009 or BPCIA. The BPCIA established a regulatory scheme authorizing the FDA to approve biosimilars and interchangeable biosimilars. As of January 1, 2019, the FDA has approved seventeen biosimilar products 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 BPCIA, 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 the FDA determines that a companion diagnostic device is essential to the safe and effective use of a novel therapeutic product or indication, the 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 FDA previously has required in vitro companion diagnostics intended to select the patients who will respond to the product candidate to obtain pre-market approval, or PMA, simultaneously with approval of the therapeutic product candidate. The PMA process, including the gathering of clinical and preclinical data and the submission to and review by the FDA, can take several years or longer. It involves a rigorous premarket review during which the applicant must prepare and provide the FDA with reasonable assurance of the device's safety and effectiveness and information about the device and its components regarding, among other things, device design, manufacturing and labeling. PMA applications are subject to an application fee, which exceeds $250,000 for most PMAs fees for medical device product review; for federal fiscal year 2019, the standard fee for review of a PMA is $322,147 and the small business fee is $80,537.

A clinical trial is typically required for a PMA application and, in a small percentage of cases, the FDA may require a clinical study in support of a 510(k) submission. A manufacturer that wishes to conduct a clinical study involving the device is subject to the FDA's IDE regulation. The IDE regulation distinguishes between significant and non-significant risk device studies and the procedures for obtaining approval to begin the study differ accordingly. Also, some types of studies are exempt from the IDE regulations. A significant risk device presents a potential for serious risk to the health, safety, or welfare of a subject. Significant risk devices are devices that are substantially important in diagnosing, curing, mitigating, or treating disease or in preventing impairment to human health. Studies of devices that pose a significant risk require both FDA and an IRB approval prior to initiation of a clinical study. Non-significant risk devices are devices that do not pose a significant risk to the human subjects. A non-significant risk device study requires only IRB approval prior to initiation of a clinical study.

After a device is placed on the market, it remains subject to significant regulatory requirements. Medical devices may be marketed only for the uses and indications for which they are cleared or approved. Device manufacturers must also establish registration and device listings with the FDA. A medical device manufacturer's manufacturing processes and those of its suppliers are required to comply with the applicable portions of the QSR, which cover the methods and documentation of the design, testing, production, processes, controls, quality assurance, labeling, packaging and shipping of medical devices. Domestic facility records and manufacturing processes are subject to periodic unscheduled inspections by the FDA. The FDA also may inspect foreign facilities that export products to the United States

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 GCP, a system for the approval of clinical trials in the EU has been implemented through national legislation of the member states. Under this system, an applicant must obtain approval from the competent national authority of an EU member

state in which the clinical trial is to be conducted, or in multiple member states if the clinical trial is to be conducted in a number of member states. Furthermore, the applicant may only start a clinical trial at a specific study site after the competent ethics committee has issued a favorable opinion. The clinical trial application, or CTA, must be accompanied by an investigational medicinal product dossier with supporting information prescribed by Directive 2001/20/EC and Directive 2005/28/EC and corresponding national laws of the member states and further detailed in applicable guidance documents.

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 become 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 will become applicable later in 2019. 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.

As in the United States, similar requirements for posting clinical trial information are present in other countries; for the members of the EU, the website EudraCT can be found at: https://eudract.ema.europa.eu/.

PRIME Designation in the EU

In March 2016, the EMA launched an initiative to facilitate development of product candidates in indications, often rare, for which few or no therapies currently exist. The PRIority MEdicines, or PRIME, scheme is intended to encourage drug development in areas of unmet medical need and provides accelerated assessment of products representing substantial innovation reviewed under the centralized procedure. Products from small- and medium-sized enterprises, or SMEs, may qualify for earlier entry into the PRIME scheme than larger companies. Many benefits accrue to sponsors of product candidates with PRIME designation, including but not limited to, early and proactive regulatory dialogue with the EMA, frequent discussions on clinical trial designs and other development program elements, and accelerated marketing authorization application assessment once a dossier has been submitted. Importantly, a dedicated Agency contact and rapporteur from the CHMP or Committee for Advanced Therapies, or CAT, are appointed early in PRIME scheme facilitating increased understanding of the product at EMA's Committee level. A kick-off meeting initiates these relationships and includes a team of multidisciplinary experts at the EMA to provide guidance on the overall development and regulatory strategies.

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.

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.

Regulatory Data Protection in the European Union

In the EU, new chemical entities approved on the basis of a complete independent data package qualify for eight years of data exclusivity upon marketing authorization and an additional two years of market exclusivity pursuant to Regulation (EC) No 726/2004, as amended, and Directive 2001/83/EC, as amended. Data exclusivity prevents regulatory authorities in the EU from referencing the innovator's data to assess a generic (abbreviated) application for a period of eight years. During the additional two year period of market exclusivity, a generic marketing authorization application can be submitted, and the innovator's data may be referenced, but no generic medicinal product can be marketed until the expiration of the market exclusivity. The overall ten year period will be extended to a maximum of eleven years if, during the first eight years of those ten years, the marketing authorization holder obtains an authorization for one or more new therapeutic indications which, during the scientific evaluation prior to authorization, is held to bring a significant clinical benefit in comparison with existing therapies. Even if a compound is considered to be a new chemical entity so that the innovator gains the prescribed period of data exclusivity, another company may market another version of the product if such company obtained marketing authorization based on an MAA with a complete independent data package of pharmaceutical tests, preclinical tests and clinical trials.

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.

Orphan drug 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. This is the case despite an earlier court opinion holding that the Orphan Drug Act unambiguously required the FDA to recognize orphan exclusivity regardless of a showing of clinical superiority.

34

Regulatory Requirements After Marketing Authorization

Following marketing authorization of a medicinal product in the EU, the holder of the authorization is required to comply with a range of requirements applicable to the manufacturing, marketing, promotion and sale of medicinal products. These include compliance with the EU's stringent pharmacovigilance or safety reporting, as well as rules potentially requiring post-authorization studies and additional monitoring obligations. In addition, the manufacturing of authorized medicinal products, for which a separate manufacturer's license is mandatory, must also be conducted in strict compliance with the applicable EU laws, regulations and guidance, including Directive 2001/83/EC, Directive 2003/94/EC, Regulation (EC) No 726/2004 and the European Commission Guidelines for Good Manufacturing Practice. These requirements include compliance with EU cGMP standards when manufacturing medicinal products and active pharmaceutical ingredients, including the manufacture of active pharmaceutical ingredients outside of the EU with the intention to import the active pharmaceutical ingredients into the EU. Finally, the marketing and promotion of authorized drugs, including industry-sponsored continuing medical education and advertising directed toward the prescribers of drugs and/or the general public, are strictly regulated in the EU notably under Directive 2001/83EC, as amended, and EU Member State laws. Direct-to-consumer advertising of prescription medicines is prohibited across the EU.

Brexit and the Regulatory Framework in the United Kingdom

On June 23, 2016, the electorate in the United Kingdom voted in favor of leaving the EU (commonly referred to as "Brexit"). Thereafter, on March 29, 2017, the country formally notified the EU of its intention to withdraw pursuant to Article 50 of the Lisbon Treaty. The withdrawal of the United Kingdom from the EU will take effect either on the effective date of the withdrawal agreement or, in the absence of agreement, two years after the United Kingdom provides a notice of withdrawal pursuant to the EU Treaty. Since the regulatory framework for pharmaceutical products in the United Kingdom. covering quality, safety and efficacy of pharmaceutical products, clinical trials, marketing authorization, commercial sales and distribution of pharmaceutical products is derived from EU directives and regulations, Brexit could materially impact the future regulatory regime which applies to products and the approval of product candidates in the United Kingdom. It remains to be seen how, if at all, Brexit will impact regulatory requirements for product candidates and products in the United Kingdom.

The United Kingdom has a period of a maximum of two years from the date of its formal notification to negotiate the terms of its withdrawal from, and future relationship with, the EU. If no formal withdrawal agreement is reached between the United Kingdom and the EU, then it is expected the United Kingdom's membership of the EU will automatically terminate two years after the submission of the notification of the United Kingdom's intention to withdraw from the EU. Discussions between the United Kingdom and the EU focused on finalizing withdrawal issues and transition agreements are ongoing. However, limited progress to date in these negotiations and ongoing uncertainty within the UK Government and Parliament sustains the possibility of the United Kingdom leaving the EU on March 29, 2019 without a withdrawal agreement and associated transition period in place, which is likely to cause significant market and economic disruption.

General Data Protection Regulation

The collection, use, disclosure, transfer, or other processing of personal data regarding individuals in the EU, including personal health data, is subject to the EU General Data Protection Regulation, or GDPR, which became effective on May 25, 2018. The GDPR is wide-ranging in scope and imposes numerous requirements on companies that process personal data, including requirements relating to processing health and other sensitive data, obtaining consent of the individuals to whom the personal data relates, providing information to individuals regarding data processing activities, implementing safeguards to protect the security and confidentiality of personal data, providing notification of data breaches, and taking certain measures when engaging third-party processors. The GDPR also imposes strict rules on the transfer of personal data to countries outside the EU, including the U.S., and permits data protection authorities to impose large penalties for violations of the GDPR, including potential fines of up to €20

million or 4% of annual global revenues, whichever is greater. The GDPR also confers a private right of action on data subjects and consumer associations to lodge complaints with supervisory authorities, seek judicial remedies, and obtain compensation for damages resulting from violations of the GDPR. Compliance with the GDPR will be a rigorous and time-intensive process that may increase the cost of doing business or require companies to change their business practices to ensure full compliance.

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 EU, 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 EU 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. EU 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 EU 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 EU. 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 EU 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 be 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;
- Foreign Corrupt Practices Act, or FCPA, which prohibits companies and their intermediaries from making, or offering or promising to make improper payments to non-U.S. officials for the purpose of obtaining or retaining business or otherwise seeking favorable treatment;
- 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 ACA, 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 U.S. 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.

By way of example, the United States and state governments continue to propose and pass legislation designed to reduce the cost of healthcare. In March 2010, the United States Congress enacted the ACA, which, among other things, includes changes to the coverage and payment for products under government health care programs. Among the provisions of the ACA of importance to our potential product candidates are:

- an annual, nondeductible fee on any entity that manufactures or imports specified branded prescription drugs and biologic agents, apportioned among these entities according to their market share in certain government healthcare programs, although this fee would not apply to sales of certain products approved exclusively for orphan indications;
- expansion of eligibility criteria for Medicaid programs by, among other things, allowing states to offer Medicaid coverage to certain individuals with income at or below 133% of the federal poverty level, thereby potentially increasing a manufacturer's Medicaid rebate liability;
- expanded manufacturers' rebate liability under the Medicaid Drug Rebate Program by increasing the minimum rebate for both branded and generic drugs and revising the definition of "average manufacturer price", or AMP, for calculating and reporting Medicaid drug rebates on outpatient prescription drug prices and extending rebate liability to prescriptions for individuals enrolled in Medicare Advantage plans;
- addressed a new methodology by which rebates owed by manufacturers under the Medicaid Drug Rebate Program are calculated for products that are inhaled, infused, instilled, implanted or injected;
- expanded the types of entities eligible for the 340B drug discount program;
- established the Medicare Part D coverage gap discount program by requiring manufacturers to provide a 50% point of sale discount off the negotiated price of applicable products to eligible beneficiaries during their coverage gap period as a condition for the manufacturers' outpatient products to be covered under Medicare Part D;
- a new Patient Centered Outcomes Research Institute to oversee, identify priorities in, and conduct comparative clinical effectiveness research, along with funding for such research;
- the Independent Payment Advisory Board, or IPAB, which has authority to recommend certain changes to the Medicare program to reduce expenditures by the program that could result in reduced payments for prescription products. However, the IPAB implementation has been not been clearly defined. The ACA provided that under certain circumstances, IPAB recommendations will become law unless Congress enacts legislation that will achieve the same or greater Medicare cost savings; and
- established the Center for Medicare and Medicaid Innovation within CMS to test innovative payment and service delivery models to lower Medicare and Medicaid spending, potentially including prescription product spending. Funding has been allocated to support the mission of the Center for Medicare and Medicaid Innovation from 2011 to 2019.

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.

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 we may obtain regulatory approval or the frequency with which any such product candidate is prescribed or used. Further, there have been several recent U.S. congressional inquiries and proposed state and federal legislation designed to, among other things, bring more transparency to drug pricing, review the relationship between pricing and manufacturer patient programs, reduce the costs of drugs under Medicare and reform government program reimbursement methodologies for drug products.

38

Since enactment of the ACA, there have been numerous legal challenges and Congressional actions to repeal and replace provisions of the law. For example, with enactment of the Tax Cuts and Jobs Act of 2017, which was signed by the President on December 22, 2017, Congress repealed the "individual mandate." The repeal of this provision, which requires most Americans to carry a minimal level of health insurance, became effective January 1, 2019. According to the Congressional Budget Office, the repeal of the individual mandate will cause 13 million fewer Americans to be insured in 2027 and premiums in insurance markets may rise. Additionally, on January 22, 2018, President Trump signed a continuing resolution on appropriations for fiscal year 2018 that delayed the implementation of certain ACA-mandated fees, including the so-called "Cadillac" tax on certain high cost employer-sponsored insurance plans, the annual fee imposed on certain health insurance providers based on market share, and the medical device excise tax on non-exempt medical devices. Further, the Bipartisan Budget Act of 2018, among other things, amends the ACA, effective January 1, 2019, to increase from 50 percent to 70 percent the point-of-sale discount that is owed by pharmaceutical manufacturers who participate in Medicare Part D and to close the coverage gap in most Medicare drug plans, commonly referred to as the "donut hole."

The Trump Administration has also taken executive actions to undermine or delay implementation of the ACA. Since January 2017, President Trump has signed two Executive Orders designed to delay the implementation of certain provisions of the ACA or otherwise circumvent some of the requirements for health insurance mandated by the ACA. One Executive Order directs 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. The second Executive Order terminates the cost-sharing subsidies that reimburse insurers under the ACA. Several state attorneys general filed suit to stop the Trump Administration from terminating the subsidies, but their request for a restraining order was denied by a federal judge in California on October 25, 2017. In addition, CMS has recently proposed regulations that would give states greater flexibility in setting benchmarks for insurers in the individual and small group marketplaces, which may have the effect of relaxing the essential health benefits required under the ACA for plans sold through such marketplaces. Further, on June 14, 2018, U.S. Court of Appeals for the Federal Circuit ruled that the federal government was not required to pay more than $12 billion in ACA risk corridor payments to third-party payors who argued were owed to them. The effects of this gap in reimbursement on third-party payors, the viability of the ACA marketplace, providers, and potentially our business, are not yet known.

Further, there have been several recent U.S. congressional inquiries and proposed federal and proposed and enacted state legislation designed to, among other things, bring more transparency to drug pricing, review the relationship between pricing and manufacturer patient programs, reduce the costs of drugs under Medicare and reform government program reimbursement methodologies for drug products. For example, there have been several recent U.S. congressional inquiries and proposed federal and proposed and enacted state legislation designed to, among other things, bring more transparency to drug pricing, review the relationship between pricing and manufacturer patient programs, reduce the costs of drugs under Medicare and reform government program reimbursement methodologies for drug products. At the federal level, Congress and the Trump administration have each indicated that it will continue to seek new legislative and/or administrative measures to control drug costs.

For example, on May 11, 2018, the Trump Administration issued a plan to lower drug prices. Under this blueprint for action, the Trump Administration indicated that the Department of Health and Human Services, or HHS, will: take steps to end the gaming of regulatory and patent processes by drug makers to unfairly protect monopolies; advance biosimilars and generics to boost price competition; evaluate the inclusion of prices in drug makers' ads to enhance price competition; speed access to and lower the cost of new drugs by clarifying policies for sharing information between insurers and drug makers; avoid excessive pricing by relying more on value-based pricing by expanding outcome-based payments in Medicare and Medicaid; work to give Part D plan sponsors more negotiation power with drug makers; examine which Medicare Part B drugs could be negotiated for a lower price by Part D plans and improving the design of the Part B Competitive Acquisition Program; update Medicare's drug-pricing dashboard to increase transparency; prohibit Part D contracts that include "gag rules" that prevent pharmacists from informing patients when they could pay less out-of-pocket by not using insurance; and require that Part D plan members be

provided with an annual statement of plan payments, out-of-pocket spending, and drug price increases. More recently, on January 31, 2019, the HHS Office of Inspector General proposed modifications to the federal Anti-Kickback Statute discount safe harbor for the purpose of reducing the cost of drug products to consumers which, among other things, if finalized, will affect discounts paid by manufacturers to Medicare Part D plans, Medicaid managed care organizations and pharmacy benefit managers working with these organizations.

At the state level, individual states are increasingly aggressive in passing legislation and implementing regulations designed to control pharmaceutical and biological product pricing, including price or patient reimbursement constraints, discounts, restrictions on certain product access and marketing cost disclosure and transparency measures, and, in some cases, designed to encourage importation from other countries and bulk purchasing. In addition, regional health care authorities and individual hospitals are increasingly using bidding procedures to determine what pharmaceutical products and which suppliers will be included in their prescription drug and other health care programs. These measures could reduce the ultimate demand for our products, once approved, or put pressure on our product pricing. We expect that additional state and federal healthcare reform measures will be adopted in the future, any of which could limit the amounts that federal and state governments will pay for healthcare products and services, which could result in reduced demand for our product candidates or additional pricing pressures.

There have been, and likely will continue to be, additional legislative and regulatory proposals at the foreign, federal, and state levels directed at broadening the availability of healthcare and containing or lowering the cost of healthcare. Such reforms could have an adverse effect on anticipated revenues 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.

Employees

As of December 31, 2018, we had 17 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.

Executive Officers of the Registrant

The following table lists the positions, names and ages of our executive officers as of March 1, 2019:

Executive Officers

Michael P. Bailey	53	Chief Executive Officer, President and Director
Matthew Dallas	43	Chief Financial Officer
Michael N. Needle	59	Chief Medical Officer
Nikhil Mehta	60	SVP Regulatory and Quality Assurance
Karuna Rubin	42	SVP and General Counsel

Michael P. Bailey was appointed President and Chief Executive Officer and a member of our Board of Directors in January 2015. Mr. Bailey joined our company in September 2010 as Chief Commercial Officer and was named 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.

Matthew Dallas was appointed Chief Financial Officer in June 2017. From February 2015 to March 2017, Mr. Dallas served as Chief Financial Officer and Treasurer of CoLucid Pharmaceuticals, Inc., a position he held through that biopharmaceutical company's initial public offering and subsequent acquisition, for approximately $960 million, by Eli Lilly and Company. From 2011 to February 2015, he served as Vice President of Finance and Treasurer of AVEO. Mr. Dallas previously worked at Genzyme Corporation from 2000 to 2011, NEN Life Sciences from 1999 to 2000, and Kimberly-Clark Corporation from 1997 to 1999 where he held various positions of increasing responsibility in finance and accounting. In November 2018, Mr. Dallas joined the board of directors of Biostage, Inc., a public biopharmaceutical company. Mr. Dallas holds a B.S. in Finance from the University of Tennessee, Knoxville.

Michael N. Needle, M.D. was appointed Chief Medical Officer in January 2015. Dr. Needle has played central roles in the development of oncology and hematology drugs including Erbitux® (cetuximab), Revlimid® (lenalidomide) and Pomalyst® (pomolidimide). Dr. Needle served as Chief Medical Officer for Array BioPharma Inc., a biopharmaceutical company, from April 2013 to September 2014. From April 2012 to April 2013, Dr. Needle was Chief Medical Officer of the Multiple Myeloma Research Foundation and Consortium (MMRF), a research organization. From 2010 to 2012, Dr. Needle was Assistant Professor of Pediatrics at the College of Physicians and Surgeons of Columbia University. From 2004 to 2010, 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. Dr. Needle also served as the Vice President of Clinical Affairs at ImClone from 2000 to 2004. Dr. Needle performed 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 B.A. in Physics and received his M.D. from SUNY Downstate Medical Center, in Brooklyn, New York.

Nikhil Mehta, Ph.D. was appointed Senior Vice President of Regulatory and Quality Assurance in November 2017. From June 2016 to September 2017, Dr. Mehta served as Executive Vice President and Chief Regulatory Strategist at Tang Capital Management, where he worked on the establishment of two biopharmaceutical companies, Odonate Therapeutics and Sentier Therapeutics. From April 2015 to June 2016, Dr. Mehta served as Global Head of Regulatory Affairs at Baxalta, a period during which the company gained approval for ADYNOVATE®, VONVENDI®, and OBIZUR. From 2010 to 2015, he was Vice President, Global Regulatory Affairs, Oncology, Hematology, Immunology and Diagnostics, at Merck & Company, where he played a key role in the development and first approval of Merck's checkpoint inhibitor KEYTRUDA. Prior to Merck, Dr. Mehta held positions of increasing responsibility within regulatory affairs at Shire HGT, ImClone Systems, Bristol-Myers Squibb and Hoffmann-La Roche, where he played key roles in the approvals of ELAPRASE®, VPRIV®, FIRAZYR® and ERBITUX. Dr. Mehta holds a Ph.D. in Chemical and Biochemical Engineering from Rutgers University.

Karuna Rubin was appointed Senior Vice President and General Counsel in February 2018. Ms. Rubin served as our Vice President, Legal Affairs and Corporate Secretary from July 2016 to January 2018, and as our Senior Corporate Counsel from July 2015 to July 2016. Prior to joining our company, Ms. Rubin was an associate at Arnold & Porter LLP from 2001 to 2006, and then again from 2008 to August 2013. From 2006 to 2008, Ms. Rubin served as Assistant General Counsel of Cenveo, Inc. Ms. Rubin received her J.D. from Columbia Law School and A.B. in International Relations from Brown University.

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 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 obtain additional funding to support our current operating plan. We have identified conditions and events that raise substantial doubt about our ability to continue as a going concern. As of December 31, 2018, we had approximately $24.4 million in cash, cash equivalents and marketable securities. In February 2019, we sold approximately 12.5 million shares of our common stock pursuant to our Leerink Sales Agreement and received approximately $7.5 million in net proceeds. Based on our available cash resources, we believe we do not have sufficient cash on hand to support current operations for at least the next twelve months from the date of filing this Annual Report on Form 10-K. This condition raises substantial doubt about our ability to continue as a going concern within one year after the date the financial statements included elsewhere in this Annual Report on Form 10-K are issued. Management’s plans in this regard are described in Note 1 of the consolidated financial statements included elsewhere in this Annual Report on Form 10-K. 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 have incurred significant losses since inception and anticipate that we will continue to incur significant operating losses for the foreseeable future. It is uncertain if we will ever attain profitability.

We have incurred a net loss of $5.3 million for the year ended December 31, 2018 and as of December 31, 2018, had an accumulated deficit of $595.0 million. To date, we have not commercialized any products or generated any material revenues from the sale of products. 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 and maintain 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 development and commercialization activities for tivozanib. For example, we estimate that the aggregate remaining costs for the TIVO-3 trial, including drug supply and distribution, could be in the range of $5.0 million to $6.0 million through 2019. We estimate that the overall cost for the TIVO-3 trial, including drug supply and distribution, could be in the range of $49.0 million to $50.0 million. Our aggregate remaining costs for the TiNivo trial in collaboration with BMS and EUSA, including tivozanib drug supply and distribution, could be in the range of $0.6 million to $0.8 million through 2019. We estimate that the overall cost for the TiNivo trial, including drug supply and distribution, could be in the range of $4.0 million to $4.6 million. BMS is providing nivolumab for the TiNivo trial. In addition, in September 2017, EUSA elected to opt-in to co-develop the TiNivo trial and paid the maximum $2.0 million for its approximate 50% share of the total trial costs.

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 believe that our approximately $24.4 million in cash, cash equivalents and marketable securities at December 31, 2018, along with approximately $7.5 million received in net proceeds from the sale of approximately 12.5 million shares of our common stock pursuant to the Leerink Sales Agreement in February 2019 and together with the extension of the interest-only period under the loan agreement with Hercules, which results in the deferment of principal payments until August 1, 2019, would allow us to fund our planned operations into the first quarter of 2020. This estimate assumes no receipt of additional milestone payments and royalties from our partners, no funding from new partnership agreements, no additional equity financings, no debt financings, no additional sales of equity under the Leerink Sales Agreement and no additional sales of equity through the exercise of our outstanding warrants. Accordingly, the timing and nature of activities contemplated for the remainder of 2019 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 researching and developing our product candidates and of conducting preclinical and clinical trials;
- the timing of, and the costs involved in, completing our clinical trials and 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, which we refer to as the 2017 Loan Agreement with Hercules, or under any other agreements with third parties;
- the cost and outcome of any legal actions against us, including the purported class action lawsuit filed against us in February 2019 described below under the heading "Part I, Item 3 – Legal Proceedings";
- the cost of commercialization activities if any of our product candidates are approved for sale, including marketing, sales and distribution costs;
- the cost of manufacturing our product candidates and any products we successfully commercialize;
- the timing, receipt and amount of sales of, or royalties on, FOTIVDA and our future products, if any; and
- our ability to continue as a going concern.

We will require additional funding to extend our planned operations. 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, Hercules may accelerate payments if we were to default under the 2017 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.

Other than the European marketing approval for tivozanib (FOTIVDA) received by our partner EUSA in August 2017, 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 and may not demonstrate the results necessary to support the filing of an NDA with the FDA or to obtain marketing approval in a particular market. For example, although we announced positive topline results for the primary endpoint of the TIVO-3 trial in November 2018, in January 2019, the FDA recommended that we not submit an NDA for tivozanib at this time as the preliminary OS results from the TIVO-3 trial did not allay its concerns about a potential detriment in OS from the TIVO-1 trial. Although we plan to make a decision whether to submit an NDA for tivozanib to the FDA following the availability of more mature OS results, we may not be able to submit our NDA in the near future or at all. Any NDA we submit to the FDA may not be accepted for submission or approved by the FDA and even if approved, we may not be able to successfully commercialize tivozanib in the United States.

Consequently, any predictions you make about our future success or viability may not be as accurate as they could be if we had more experience developing and commercializing our product candidates.

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 concluded a settlement with the SEC, but the SEC’s action against our former officer may not be concluded.

In 2016, 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 FDA, on May 11, 2012, that we conduct an additional clinical trial with respect to tivozanib. The SEC also named three of our former officers as defendants in the same lawsuit. The SEC and two of our former officers settled. In November 2018, the District Court jury ruled against the remaining former officer. However, that individual may appeal and has 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.

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

We and certain of our present officers and a former officer, were named as defendants in a purported class action lawsuit filed on February 25, 2019 that generally alleges that we and the officers violated Sections 10(b) and/or 20(a) of the Securities Exchange Act of 1934, as amended, and Rule 10b-5 promulgated thereunder by making allegedly false and/or misleading statements and/or failing to disclose that the TIVO-3 trial was inadequately designed to address the OS concerns from the TIVO-1 trial, that tivozanib had insufficient survival data to meet FDA approval following its initial 2013 rejection, and that this lack of sufficient survival data would put tivozanib at greater risk of delayed FDA approval. The complaint seeks unspecified damages, interest, attorneys’ fees, and other costs.

We intend to engage in a vigorous defense of this lawsuit. However, we are unable to predict the outcome of this matter at this time. Moreover, any conclusion of this matter 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.

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 and maintain 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.

Other than the European marketing approval for tivozanib received by our partner EUSA in August 2017, 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 North America 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 design, 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 the contract research organizations, or CROs, we have hired to manage our clinical studies, as well as that of our collaborators and other 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. For example, the recommendation of the FDA in January 2019 that we not file an NDA for tivozanib with the preliminary OS results from the TIVO-3 trial has caused us to delay our previously announced timeline with respect to such filing. 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 we fail to develop and commercialize other product candidates, we may be unable to grow our business.

Although the development and commercialization of tivozanib is our primary focus, as part of our growth strategy, we are developing a pipeline of product candidates. These other product candidates will require additional, time-consuming and costly development efforts, by us or by our collaborators, prior to commercial sale, including preclinical studies, clinical trials and approval by the FDA and/or applicable foreign regulatory authorities. All product candidates are prone to the risks of failure that are inherent in pharmaceutical product development, including

the possibility that the product candidate will not be shown to be sufficiently safe and effective for approval by regulatory authorities. In addition, we cannot assure you that any such products that are approved will be manufactured or produced economically. Successfully commercialized or widely accepted in the marketplace or be more effective than other commercially available alternatives.

If preclinical or clinical trials of any product candidates that we or our collaborators may develop fail to demonstrate satisfactory 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.

Preclinical and 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 preclinical and 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 preclinical or clinical evaluation due to a variety of factors, including the size, duration, design, measurements, conduct or analysis of our preclinical and clinical trials. Conversely, as a result of the same factors, our preclinical or 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 preclinical or 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 preclinical or 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 recommendation or 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 increase the needed enrollment size for the clinical trial, extend the clinical trial's duration, or drop the patients from the final efficacy analysis for the clinical trial, which can negatively affect the statistical power of the results;
- our decision, or a decision by regulators or institutional review boards, that may require us to 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.

47

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; and
- competing clinical trials.

In addition, participation in our clinical trials will be affected by 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. For example, at the request of the FDA, we have updated the forms used to obtain consent from patients in ongoing and future trials with tivozanib to include information about the preliminary OS results from the TIVO-3 trial as well as the other tivozanib clinical trial OS results to date. These results may impact the interest of clinicians and patients in participating in future clinical trials with tivozanib.

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.

We are conducting, and intend in the future to conduct, clinical trials for certain of our product candidates at sites outside the United States. The FDA may not accept data from trials conducted in such locations and the conduct of trials outside the United States could subject us to additional delays and expense.

We are conducting, and intend in the future to conduct, one or more of our clinical trials with one or more trial sites that are located outside the United States. Although the FDA may accept data from clinical trials conducted outside the United States, acceptance of these data is subject to certain conditions imposed by the FDA. For example, the clinical trial must be well designed and conducted and performed by qualified investigators in accordance with good clinical practice. The FDA must be able to validate the data from the trial through an onsite inspection if necessary. The trial population must also have a similar profile to the U.S. population, and the data must be applicable to the U.S. population and U.S. medical practice in ways that the FDA deems clinically meaningful, except to the extent the disease being studied does not typically occur in the United States. In addition, while these clinical trials are subject to the applicable local laws, FDA acceptance of the data will be dependent upon its determination that the trials also complied with all applicable U.S. laws and regulations. There can be no assurance that the FDA will accept data from trials conducted outside of the United States. If the FDA does not accept the data from any trial that we conduct outside the United States, it would likely result in the need for additional trials, which would be costly and time-consuming and delay or permanently halt our development of our product candidates.

In addition, the conduct of clinical trials outside the United States could have a significant adverse impact on us. Risks inherent in conducting international clinical trials include:

- clinical practice patterns and standards of care that vary widely among countries;
- non-U.S. regulatory authority requirements that could restrict or limit our ability to conduct our clinical trials;
- administrative burdens of conducting clinical trials under multiple non-U.S. regulatory authority schema;
- foreign exchange fluctuations; and
- diminished protection of intellectual property in some countries.

Results of early clinical trials may not be predictive of results of later clinical trials.

The outcome of early clinical trials, such as our phase 1b/2 TiNivo trial, may not be predictive of the success of later 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. In addition, interim results and analyses of clinical trials do not necessarily predict the final results or the success of a trial once it is complete. For example, the preliminary OS data for our TIVO-3 trial of data collected through October 4, 2019, and subsequently announced in November 2019, showed a hazard ratio of 1.06 (p-value=0.69); in January 2019, we revised the hazard ratio for the preliminary OS data to 1.12 (p-value=0.44) to reflect the survival status of a group of patients that had previously been lost to follow-up. We cannot say at this time the degree to which these interim results will be predictive of the final trial results.

While the design of a clinical trial may help to establish whether its results will support approval of a product, 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. For example, in June 2013, the FDA issued a complete response letter informing us that it would not approve tivozanib for the first-line treatment of 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 tivozanib does not adversely affect OS. Our current TIVO-3 clinical trial was designed to address the FDA's concern about the negative OS trend expressed in the complete response letter from June 2013 regarding the TIVO-1 trial. However, in January 2019, the FDA recommended that we not submit an NDA for tivozanib at this time as the preliminary OS results from the TIVO-3 trial did not allay its concerns about a potential detriment in OS from the TIVO-1 trial. Although we plan to make a decision whether to submit an NDA for tivozanib to the FDA following the availability of more mature OS results, the TIVO-3 trial could fail to achieve OS results that are satisfactory to the FDA, or could otherwise be rejected by the FDA as a basis for marketing approval for another reason.

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 may not obtain marketing approvals for our product candidates.

We may not obtain marketing approval for our product candidates. It is possible that the FDA or comparable foreign regulatory agencies 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. In June 2013, for example, the FDA issued a complete response letter informing us that it would not approve tivozanib for the first-line treatment of 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 tivozanib does not adversely affect OS. Our TIVO-3 clinical trial was designed to address the FDA's concern about the negative OS trend expressed in the complete response letter from June 2013. Although the TIVO-3 trial met its primary endpoint for PFS, the analysis of the secondary endpoint of OS was not mature at the time of the final PFS analysis, with approximately 50% of potential

OS events having been reported. After taking into account the survival status of a group of patients that were previously lost to follow-up, the preliminary OS analysis showed a hazard ratio of 1.12 and a p-value of 0.44. In January 2019, the FDA recommended that we not submit an NDA for tivozanib at this time as the preliminary OS results from the TIVO-3 trial did not allay its concerns about a potential detriment in OS from the TIVO-1 trial. If the TIVO-3 trial does not achieve a final OS result that is satisfactory to the FDA, or the FDA does not otherwise find the results of the TIVO-3 trial to adequately demonstrate a favorable risk-benefit profile for tivozanib in RCC, then the TIVO-3 trial could be rejected by the FDA as a basis for marketing approval of tivozanib.

If the FDA or other comparable foreign regulatory agency does not accept or approve any application to market and sell any of our product candidates, such regulators may require that we conduct additional clinical trials, preclinical studies or manufacturing validation studies and submit that data before they 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 or other foreign 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 certain 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, any of 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, and could cause regulatory authorities to take certain regulatory actions.

Clinical trials of our product candidates will be conducted in carefully defined subsets of patients who have agreed to participate. 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, or any of our collaborators, 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, or any of our collaborators, 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, or any of our collaborators, 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.

In August 2017, the European Commission granted marketing authorization to EUSA for tivozanib in all 28 countries of the EU, Norway and Iceland. Tivozanib is sold under the brand name FOTIVDA and is approved for the first-line treatment of adult patients with RCC and for adult patients who are VEGFR and mTOR pathway inhibitor-naïve following disease progression after one prior treatment with cytokine therapy for RCC. In January 2019, we were informed by EUSA that the CHMP requested the topline data results from our TIVO-3 trial for review at the CHMP’s January 2019 plenary meeting under its post-authorization monitoring procedures. Subsequently, EUSA has informed us that the CHMP has requested additional data analysis from our TIVO-3 trial. If the EMA finds that the results from the TIVO-3 trial raise questions on the safety or efficacy of FOTIVDA and the risk-benefit assessment on which the marketing authorization for FOTIVDA in the EU was based, it could take certain post-authorization measures with regards to FOTIVDA such as requiring EUSA to conduct additional post-authorization studies, or risk management measures as part of an extended pharmacovigilance monitoring, or a change of the labeling/use instructions for FOTIVDA. If its concerns would not be addressed by other post-authorization measures, the EMA/European Commission could also determine to change, suspend or revoke the previously granted central marketing authorization for FOTIVDA. Any such actions taken by the European regulatory authorities with respect to the marketing authorization for FOTIVDA could have a material adverse effect on our ability to receive milestone, royalty or other payments from EUSA related to the approval and/or sales of FOTIVDA and on our business, operations and prospects.

50

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. There are already a number of therapies on the market competitive to tivozanib, as well as our other product candidates, in indications we intend to target.

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;
- the timing of market introduction of our approved products as well as competitive products;
- adverse publicity about the product or favorable publicity about competitive products;
- potential product liability claims;
- 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.

We may expend our limited resources to pursue a particular product candidate or indication and fail to capitalize on product candidates or indications that may be more profitable or for which there is a greater likelihood of success.

Because we have limited financial and managerial resources, we intend to focus on developing product candidates for specific indications that we identify as most likely to succeed, in terms of their potential for marketing approval and commercialization, as well as those that are most aligned with our strategic goals. As a result, we may forego or delay pursuit of opportunities with other product candidates or for other indications that may prove to have greater commercial potential.

Our resource allocation decisions may cause us to fail to capitalize on viable commercial products or profitable market opportunities. Our spending on current and future research and development programs and product candidates for specific indications may not yield any commercially viable product candidates. If we do not accurately evaluate the commercial potential or target market for a particular product candidate, we may relinquish valuable rights to that product candidate through collaboration, licensing or other royalty arrangements in cases in which it would have been more advantageous for us to retain sole development and commercialization rights to the product candidate.

51

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 limited experience as an organization in the sales, marketing, and distribution of pharmaceutical products. Our licensee EUSA has been responsible for the sales, marketing, and distribution efforts associated with the commercial launch of tivozanib in certain European countries. 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, if 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 such as our collaboration with EUSA, our product revenues or the profitability of these products 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, or of different types of products targeting the same indications we are pursuing. A number of multinational pharmaceutical companies, as well as large biotechnology companies, including, but not limited to, Amgen Inc., ArQule, Inc., AstraZeneca, Bayer, BMS, Eisai, Lilly, Exelixis, Gilead Sciences, Inc., GSK, Helsinn, XBiotech Inc., Incyte, Janssen Pharmaceuticals, Inc. (a division of Johnson and Johnson), Jazz Pharmaceuticals plc, Merck, NGM Bio, Novartis, Pfizer and Roche are pursuing development in diseases we focus on or are currently developing or marketing pharmaceuticals that target VEGFR, HGF/c-Met, ErbB3, GDF15/GFRAL, Notch 3 or other pathways on which we may focus. 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, or having the same biological targets, as the product candidates we are developing, including with respect to RCC. 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 VEGFR pathway as a part or all of their inhibitory mechanism. Eight of the FDA-approved VEGFR pathway inhibitors are oral small molecule receptor TKIs. Many of the approved VEGFR 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 VEGFR pathway. The emergence of PD-1/PD-L1 inhibitor and other immune system-targeted therapies, both alone and in combination, present additional competition for tivozanib. We are aware of several phase 3 registration studies evaluating PD-1/PD-L1 inhibitors in combination with VEGFR TKIs in RCC, as well as combinations of PD-1 agents with other immune therapies for RCC. The FDA approved the combination of Opdivo and Yervoy for first-line RCC patients with intermediate or poor risk prognosis in April 2018. In addition, the IMmotion151 phase 3 combination study of bevacizumab and atezolizumab versus sunitinib in first-line RCC reported positive results for one of the co-primary endpoints, PFS; the JAVELIN Renal 101 phase 3 combination study of axitinib and avelumab versus sunitinib in first-line RCC reported positive results for one of the co-primary endpoints, PFS in PD-L1+ patients; and the KEYNOTE-426 phase 3 combination study of axitinib and pembrolizumab versus sunitinib in first-line RCC reported positive results for both primary endpoints of PFS and OS. Phase 3 studies for the treatment of HCC have been initiated for the combination of bevacizumab and atezolizumab as well as the combination of lenvatinib and pembrolizumab. If any of these additional combinations are approved, they could present additional competition for tivozanib.

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 or 3 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 oncology; however, a number of agents for applications in oncology are being explored which target the Notch 3 receptor and may inhibit other Notch receptors.

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. For example, our European licensee for tivozanib, EUSA, is currently in the process of seeking reimbursement approval for tivozanib in many of the countries in which tivozanib has been approved. 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 clinical 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;
- significant 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;
- injury to our reputation and negative media attention; and
- 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. We will need to increase our insurance coverage if we commercialize any product that receives marketing approval. 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. The cost of any such product liability litigation or other proceeding, even if resolved in our favor, could be substantial. In addition, insurance coverage is becoming increasingly expensive. If we are unable to maintain sufficient insurance coverage at an acceptable cost or to otherwise protect against potential product liability claims, it could prevent or inhibit the development and commercial production and sale of our product candidates, which could harm our business, financial condition, results of operations and prospects.

Risks Related to Our Dependence on Third Parties

We rely on third parties, such as 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 rely on CROs and other third parties to perform many of the functions 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 and 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, including GCPs, 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, process and analyze is compromised for any reason, including 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 experience delays or may fail to 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 certain 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. Other risks of our reliance on third-party manufacturers include the possible mislabeling of clinical supplies, potentially resulting in the wrong dose amounts being supplied or active drug or placebo not being properly identified; the possibility of clinical supplies not being delivered to clinical sites on time, leading to clinical trial interruptions, or of drug supplies not being distributed to commercial vendors in a timely manner, resulting in lost sales; and the possible misappropriation of our proprietary information, including our trade secrets and know-how. In addition, the FDA and other regulatory authorities require that our product candidates be manufactured according to current good manufacturing practices, or cGMPs. 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 and potential commercial manufacturing. There are a small number of suppliers of raw and starting materials that we use to manufacture our product candidates. Such suppliers may not sell these 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 these materials by our manufacturers. Any significant delay in the supply of a product candidate or the raw material components thereof for an ongoing clinical trial or potential commercial launch 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 there could be a shortage in supply, which would impair our ability to generate revenues from the sale of our product candidates.

Because of the complex nature of many of our early stage compounds and product candidates, our manufacturers may not be able to manufacture such compounds and product candidates at a cost or quantity or in the timeframe necessary to develop and commercialize the 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 may need to increase their scale of production or we may 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 their 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 our own. Our current partners and licensees can terminate their agreements with us under various conditions, including without cause, at which point they would no longer continue to develop our products. For example, following a change in strategic priorities, Novartis terminated the Novartis License Agreement for our AV-380 program in August 2018 without cause. During the term of the Novartis License Agreement, Novartis had been responsible for the costs and development of the AV-380 program worldwide. Novartis is currently in the process of transferring the AV-380 program and returning the AV-380 drug supply back to us. We are working to initiate preclinical toxicology studies mid-2019 to support a potential IND filing with the FDA.

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 or any other reason, 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, or the scope of our patient protection could be insufficiently broad, 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 United States under the Hatch-Waxman Act, by SPCs in certain European countries, 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 materially reduced.

The U.S. patent covering the tivozanib 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, could 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. In addition, SPCs have been granted in Germany, Italy, Portugal, Spain and Sweden, and are pending in 9 additional European countries, including Belgium, Denmark, France, Great Britain, and the Netherlands, for the corresponding patents in those countries that cover the tivozanib molecule, which, if granted, could extend the term of the patent in each of those countries up to 2027. 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 the patent rights covering tivozanib or its use can be enforced 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 USPTO, 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 that contains broad claims related to the use of a TKI 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 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. 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 use 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 which we have licensed and on which our business depends or may prosecute them in a manner not in the best interests of our business. 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, such as 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.

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 and result in a material disruption of our product development programs.

We could be subject to risks caused by misappropriation, misuse, leakage, falsification or intentional or accidental release or loss of information maintained in the information systems and networks of our company, including personal information of our employees. In addition, outside parties may attempt to penetrate our systems or those of our partners or fraudulently induce our employees or employees of our partners to disclose sensitive information to gain access to our data. Like other companies, we may experience threats to our data and systems, including malicious codes and computer viruses, cyber-attacks, or other system failures. Any system failure, accident or security breach that causes interruptions in our operations, for us or our partners, could result in a material disruption of our product development programs and business operations, in addition to possibly requiring substantial expenditures of resources to remedy. For example, the loss of clinical trial data from completed clinical trials could result in delays in our regulatory approval efforts and we could incur significant increases in costs to recover or reproduce the data. To the extent that any disruption or security breach results in a loss of, or damage to, our data or applications, or inappropriate public disclosure of confidential or proprietary information, we may incur liabilities and the further development of our product candidates may be delayed. In addition, we may not have adequate insurance coverage to provide compensation for any losses associated with such events.

The number and complexity of these threats continue to increase over time. If a material breach of our security or that of our partners occurs, the market perception of the effectiveness of our security measures could be harmed, we could

lose business and our reputation and credibility could be damaged. We could be required to expend significant amounts of money and other resources to repair or replace information systems or networks. Although we develop and maintain systems and controls designed to prevent these events from occurring, and we have a process to identify and mitigate threats, the development and maintenance of these systems, controls and processes is costly and requires ongoing monitoring and updating as technologies change and efforts to overcome security measures become more sophisticated. Moreover, despite our efforts, the possibility of these events occurring cannot be eliminated entirely.

Additionally, the collection, use, disclosure, transfer, or other processing of personal data regarding individuals in the EU, including personal health data, is subject to the EU General Data Protection Regulation, or GDPR, which became effective on May 25, 2018. The GDPR is wide-ranging in scope and imposes numerous requirements on companies that process personal data, including requirements relating to processing health and other sensitive data, obtaining consent of the individuals to whom the personal data relates, providing information to individuals regarding data processing activities, implementing safeguards to protect the security and confidentiality of personal data, providing notification of data breaches, and taking certain measures when engaging third-party processors. The GDPR also imposes strict rules on the transfer of personal data to countries outside the EU, including the United States, and permits data protection authorities to impose large penalties for violations of the GDPR, including potential fines of up to €20 million or 4% of annual global revenues, whichever is greater. The GDPR also confers a private right of action on data subjects and consumer associations to lodge complaints with supervisory authorities, seek judicial remedies, and obtain compensation for damages resulting from violations of the GDPR. Compliance with the GDPR will be a rigorous and time-intensive process that may increase our cost of doing business or require us to change our business practices, and despite those efforts, there is a risk that we may be subject to fines and penalties, litigation, and reputational harm in connection with any European activities.

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.
- Our pending patent applications might 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 or our strategic partners' existing or potential 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 involves both technological complexity and legal complexity. Therefore, obtaining and enforcing biopharmaceutical patents is costly, time-consuming and inherently uncertain. In addition, several events in the last decade 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 United States. The patent law introduces changes including a first-to-file system for determining which inventors may be entitled to receive patents, and a 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 have only limited experience in filing and supporting the applications necessary to gain marketing approvals and expect to rely on third-party CROs 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. For example, in June 2013, the FDA issued a complete response letter informing us that it would not approve tivozanib for the first-line treatment of RCC based solely on the data from the TIVO-1 trial. Further, in January 2019, the FDA recommended that we not submit an NDA for tivozanib at this time as the preliminary OS results from the TIVO-3 trial did not allay its concerns about a potential detriment in OS from the TIVO-1 trial. Although the TIVO-3 trial met its primary endpoint of PFS, if additional data does not sufficiently improve the OS results, we may not be able to obtain marketing approval from the FDA to successfully commercialize tivozanib in the United States.

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 EU 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 must 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 particular market.

Additionally, on June 23, 2016, the electorate in the United Kingdom voted in favor of leaving the EU, commonly referred to as Brexit. On March 29, 2017, the country formally notified the EU of its intention to withdraw pursuant to Article 50 of the Lisbon Treaty. Since a significant proportion of the regulatory framework in the United Kingdom is derived from EU directives and regulations, the referendum could materially impact the regulatory regime with respect to the approval of our product candidates in the United Kingdom or the