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.
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References to AVEO

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

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," "intend," "may," "might," "plan," "project," "should," "target," "will," "would" or other words that convey uncertainty of future events or 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;

- 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

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.

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.

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.

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.

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.

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.

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 EU. Any delay in obtaining, or an inability to obtain, any marketing approvals, as a result of Brexit or otherwise, would prevent us from commercializing our product candidates in the United Kingdom and/or the EU and restrict our ability to generate revenue and achieve and sustain profitability. If any of these outcomes occur, we may be forced to restrict or delay efforts to seek regulatory approval in the United Kingdom and/or the EU for our product candidates, which could significantly and materially harm our business.

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.

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

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

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

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

On August 3, 2017, Congress passed the FDA Reauthorization Act of 2017, or FDARA. FDARA, among other things, codified the FDA’s pre-existing regulatory interpretation, to require that a drug sponsor demonstrate the clinical superiority of an orphan drug that is otherwise the same as a previously approved drug for the same rare disease in order to receive orphan drug exclusivity. The new legislation reverses prior precedent holding that the Orphan Drug Act unambiguously requires that the FDA recognize the orphan exclusivity period regardless of a showing of clinical superiority. The FDA may further reevaluate the Orphan Drug Act and its regulations and policies. We do not know if, when, or how the FDA may change the orphan drug regulations and policies in the future, and it is uncertain how any changes might affect our business. Depending on what changes the FDA may make to its orphan drug regulations and policies, our business could be adversely impacted.

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

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

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

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

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

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

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

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

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

- restrictions on such products, manufacturers or manufacturing processes;
- restrictions on the labeling or marketing of a product;
- restrictions on distribution or use of a product;
- requirements to conduct post-marketing studies or clinical trials;
- warning letters or untitled letters;

- withdrawal of the products from the market;
- refusal to approve pending applications or supplements to approved applications that we submit;
- recall of products;
- damage to relationships with collaborators;
- unfavorable press coverage and damage to our reputation;
- fines, restitution or disgorgement of profits or revenues;
- suspension or withdrawal of marketing approvals;
- refusal to permit the import or export of our products;
- product seizure;
- injunctions or the imposition of civil or criminal penalties; and
- litigation involving patients using our products.

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

The efforts of the Trump Administration to pursue regulatory reform may limit the FDA's ability to engage in oversight and implementation activities in the normal course, and that could negatively impact our business.

The Trump Administration has taken several executive actions, including the issuance of a number of executive orders, that could impose significant burdens on, or otherwise materially delay, the FDA's ability to engage in routine regulatory and oversight activities such as implementing statutes through rulemaking, issuance of guidance, and review and approval of marketing applications. On January 30, 2017, President Trump issued an executive order, applicable to all executive agencies, including the FDA, that requires that for each notice of proposed rulemaking or final regulation to be issued in fiscal year 2017, the agency shall identify at least two existing regulations to be repealed, unless prohibited by law. These requirements are referred to as the "two-for-one" provisions. This executive order includes a budget neutrality provision that requires the total incremental cost of all new regulations in the 2017 fiscal year, including repealed regulations, to be no greater than zero, except in limited circumstances. For fiscal years 2018 and beyond, the executive order requires agencies to identify regulations to offset any incremental cost of a new regulation. In interim guidance issued by the Office of Information and Regulatory Affairs within the Office of Management and on February 2, 2017, the Trump Administration indicates that the "two-for-one" provisions may apply not only to agency regulations, but also to significant agency guidance documents. It is difficult to predict how these requirements will be implemented, and the extent to which they will impact the FDA's ability to exercise its regulatory authority. If these executive actions impose constraints on FDA's ability to engage in oversight and implementation activities in the normal course, our business may be negatively impacted.

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

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

- the federal Anti-Kickback Statute prohibits, among other things, persons from knowingly and willfully soliciting, offering, receiving or providing remuneration, directly or indirectly, in cash or in kind, to induce or reward, or in return for, either the referral of an individual for, or the purchase, order or recommendation or arranging of, any good or service, for which payment may be made under a federal healthcare program such as Medicare and Medicaid;
- the federal False Claims Act imposes criminal and civil penalties, including through civil whistleblower or qui tam actions, against individuals or entities for, among other things, knowingly presenting, or causing to be presented, false or fraudulent claims for payment by a federal healthcare program or making a false statement or record material to payment of a false claim or avoiding, decreasing or concealing an obligation to pay money to the federal government, with potential liability including mandatory treble damages and significant per-claim penalties, currently set at $10,781 to $21,563 per false claim;

- the federal Health Insurance Portability and Accountability Act of 1996, or HIPAA, imposes criminal and civil liability for executing a scheme to defraud any healthcare benefit program or making false statements relating to healthcare matters;
- HIPAA, as amended by the Health Information Technology for Economic and Clinical Health Act and its implementing regulations, also imposes obligations, including mandatory contractual terms, with respect to safeguarding the privacy, security and transmission of individually identifiable health information;
- the federal Physician Payments Sunshine Act requires applicable manufacturers of covered products to annually report to Centers for Medicare and Medicaid Services, or CMS, (i) payments and other transfers of value to physicians and teaching hospitals, and (ii) certain physician ownership or investment interests; and
- analogous state and foreign laws and regulations, such as state anti-kickback and false claims laws and transparency statutes, may apply to sales or marketing arrangements and claims involving healthcare items or services reimbursed by third-party payors, including private insurers.

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

If our operations are found to be in violation of any of the laws described above or any governmental regulations that apply to us, we may be subject to penalties, including civil and criminal penalties, damages, fines, individual imprisonment, integrity obligations, exclusion from funded healthcare programs and the curtailment or restructuring of our operations. Any such penalties could adversely affect our financial results. We are developing and implementing a corporate compliance program designed to ensure that we will market and sell any future products that we successfully develop from our product candidates in compliance with all applicable laws and regulations, but we cannot guarantee that this program will protect us from governmental investigations or other actions or lawsuits stemming from a failure to be in compliance with such laws or regulations. If any such actions are instituted against us and we are not successful in defending ourselves or asserting our rights, those actions could have a significant impact on our business, including the imposition of significant fines or other sanctions.

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

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

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

In March 2010, President Obama signed into law the Patient Protection and Affordable Care Act, as amended by the Health Care and Education Affordability Reconciliation Act, or collectively the ACA. Among the provisions of the ACA of potential importance to our business and our product candidates are the following:

- an annual, non-deductible fee on any entity that manufactures or imports specified branded prescription products and biologic agents;
- an increase in the statutory minimum rebates a manufacturer must pay under the Medicaid Drug Rebate Program;
- 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;
- expansion of healthcare fraud and abuse laws, including the civil False Claims Act and the federal Anti-Kickback Statute, new government investigative powers and enhanced penalties for noncompliance;
- a new Medicare Part D coverage gap discount program, in which manufacturers must agree to offer 50% point-of-sale discounts off negotiated prices of applicable brand products to eligible beneficiaries during their coverage gap period, as a condition for the manufacturer's outpatient products to be covered under Medicare Part D;
- extension of manufacturers' Medicaid rebate liability to individuals enrolled in Medicaid managed care organizations;
- expansion of eligibility criteria for Medicaid programs;
- expansion of the entities eligible for discounts under the Public Health Service pharmaceutical pricing program;
- new requirements to report certain financial arrangements with physicians and teaching hospitals;
- a new requirement to annually report product samples that manufacturers and distributors provide to physicians;
- a new Patient-Centered Outcomes Research Institute to oversee, identify priorities in, and conduct comparative clinical effectiveness research, along with funding for such research;
- a new 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; and
- established the Center for Medicare and Medicaid Innovation within CMS to test innovative payment and service delivery models.

In addition, other legislative changes have been proposed and adopted since the ACA was enacted. 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 2013 through 2021, was unable to reach required goals, thereby triggering the legislation's automatic reduction to several government programs. These changes included aggregate reductions to 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. The American Taxpayer Relief Act of 2012, among other things, reduced Medicare payments to several providers and increased the statute of limitations period for the government to recover overpayments to providers from three to five years. These new laws may result in additional reductions in Medicare and other healthcare funding and otherwise affect the prices we may obtain for any of our product candidates for which we may obtain regulatory approval or the frequency with which any such product candidate is prescribed or used.

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 on 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. Further, each chamber of Congress has put forth multiple bills designed to repeal or repeal and replace portions of the ACA. Although none of these measures has been enacted by Congress to date, Congress may consider other legislation to repeal and replace elements of the ACA. Congress will likely consider other legislation to replace elements of the ACA, during the next Congressional session. It is possible that repeal and replacement initiatives, if enacted into law, could ultimately result in fewer individuals having health insurance coverage or in individuals having insurance coverage with less generous benefits. While the timing and scope of any potential future legislation to repeal and replace ACA provisions is highly uncertain in many respects, it is also possible that some of the ACA provisions that generally are not favorable for the research-based pharmaceutical industry could also be repealed along with ACA coverage expansion provision. We will continue to evaluate the effect that the ACA and its possible repeal and replacement could have on our business.

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.

The costs of prescription pharmaceuticals has also been the subject of considerable discussion in the United States, and members of Congress and the Trump Administration have stated that they will address such costs through new legislative and administrative measures. To date, there have been several recent U.S. congressional inquiries and proposed and enacted 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. At the federal level, the Trump administration's budget proposal for fiscal year 2019 contains further drug price control measures that could be enacted during the 2019 budget process or in other future legislation, including, for example, measures to permit Medicare Part D plans to negotiate the price of certain drugs under Medicare Part B, to allow some states to negotiate drug prices under Medicaid, and to eliminate cost sharing for generic drugs for low-income patients. While any proposed measures will require authorization through additional legislation to become effective, Congress and the Trump administration have each indicated that it will continue to seek new legislative and/or administrative measures to control drug costs. At the state level, legislatures are increasingly 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.

Specifically, 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 Administration issued a plan to lower drug prices. Under this blueprint for action, the Administration indicated that the Department of Health and Human Services (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.

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

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

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

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

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

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

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

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

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

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

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

Disruptions at the FDA and other government agencies could prevent new products and services from being developed or commercialized in a timely manner or otherwise prevent those agencies from performing normal business functions on which the operation of our business may rely, which could negatively impact our business.

Disruptions at the FDA and other agencies may prolong the time necessary for new drugs to be reviewed and/or approved by necessary government agencies, which would adversely affect our business. For example, over the last several years, the U.S. government has shut down several times and certain regulatory agencies, such as the FDA, have had to furlough critical employees and stop critical activities. If a prolonged government shutdown occurs, it could significantly impact the ability of the FDA to timely review and process our regulatory submissions, which could have a material adverse effect on our business.

Risks Related to Employee Matters and Managing Potential Growth

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

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

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

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

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

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

Risks Related to Ownership of Our Common Stock

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

Our common stock is currently listed for quotation on the Nasdaq Capital Market. We are required to meet specified requirements to maintain our listing on the Nasdaq Capital Market, including, among other things, a minimum bid price of $1.00 per share. From January 31, 2019 to the date of this Annual Report, the bid price for our common stock had closed below the minimum $1.00 per share requirement for continued inclusion on the Nasdaq Capital Market. If we fail to satisfy the Nasdaq Capital Market's continued listing requirements, we may transfer to the OTC Bulletin Board. Having our common stock trade on the OTC Bulletin Board could adversely affect the liquidity of our common stock. Any such transfer could make it more difficult to dispose of, or obtain accurate quotations for the price of, our common stock, and there also would likely be a reduction in our coverage by securities analysts and the news media, which could cause the price of our common stock to decline further. We may also face other material adverse consequences in such event, such as negative publicity, a decreased ability to obtain additional financing, diminished investor and/or employee confidence, and the loss of business development opportunities, any of which may contribute to a further decline in our stock price.

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

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

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

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

Periods of volatility in the market for a company's stock are often followed by litigation against the company. For example, following our May 2, 2013 announcement regarding the vote of the Oncologic Drugs Advisory Committee of the FDA, we and certain of our former officers and directors were involved in a number of legal proceedings, and more recently, in February 2019, we and certain of our present officers and a former officer were named as defendants in a purported class action lawsuit following our announcement of TIVO-3 data. See Part I, Item 3 of this report under the heading "Legal Proceedings." These proceedings, and other litigation, if instituted against us, could result in substantial costs and diversion of management's attention and resources, which could materially and adversely affect our business and financial condition.

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

We set goals, and make public statements regarding our expected timing for certain accomplishments, such as statements we have made about the initiation and completion of clinical trials, filing and approval of regulatory applications and other developments and milestones under our research and development programs and those of our partners and collaborators for tivozanib, ficlatuzumab, AV-203, AV-380 and the AV-353 platform. The actual timing of these events can vary significantly due to a number of factors, including, without limitation, delays or failures in our preclinical studies or clinical trials, insufficient data or unsatisfactory results from trials, the amount of time, effort and resources committed to our programs and the uncertainties inherent in the regulatory approval process. As a result, there can be no assurance that our preclinical studies and clinical trials will advance or be completed in the time frames we expect or announce, that we will make regulatory submissions or receive regulatory approvals as planned or that we will be able to adhere to our currently anticipated schedule for the achievement of key milestones under any of our programs. If we fail to achieve one or more of the events described above as planned, our business could be materially adversely affected and the price of our common stock could decline.

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

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

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

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

- the status of our clinical development programs;
- the level of expenses incurred in connection with our clinical development programs, including development and manufacturing costs relating to our clinical development candidates;
- the implementation of restructuring and cost-savings strategies;
- the implementation or termination of collaboration, licensing, manufacturing or other material agreements with third parties, and non-recurring revenue or expenses under any such agreement;
- costs associated with lawsuits against us or other litigation in which we may become involved, including the purported class action lawsuit described elsewhere in this Annual Report on Form 10-K under “Part I, Item 3 – Legal Proceedings”;
- changes in our 2017 Loan Agreement with Hercules, including the existence of any event of default that may accelerate payments due thereunder;
- non-cash changes in fair value related to re-valuations of our outstanding warrant liability as a result of fluctuations in our stock price; and
- compliance with regulatory requirements.

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

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

As widely reported, global credit and financial markets have been experiencing extreme volatility, and in some cases, disruptions, over the past several years. Although certain of these trends have recently showed signs of reversing, there can be no assurance that rapid or extended periods of deterioration in credit and financial markets and confidence in economic conditions will not occur. Our general business strategy may be adversely affected by external economic conditions and a volatile business environment or unpredictable and unstable market conditions. If the equity and credit markets are not favorable at any time we seek to raise capital, it may make any necessary debt or equity financing more difficult, more costly, and more dilutive. Failure to secure any necessary financing in a timely manner and on favorable terms could have a material adverse effect on our growth strategy, financial performance and stock price and could require us to delay or abandon clinical development plans. In addition, there is a risk that one or more of our current service providers, manufacturers or other partners may not survive economically turbulent times, which could directly affect our ability to attain our operating goals on schedule and on budget.

At December 31, 2018, we had approximately $24.4 million of cash, cash equivalents and marketable securities consisting of cash on deposit with banks, a U. S. government money market fund and corporate debt securities, including commercial paper. As of the date of this report, we are not aware of any downgrades, material losses, or other significant deterioration in the fair value of our cash equivalents. However, no assurance can be given that deterioration in conditions of the global credit and financial markets would not negatively impact our current portfolio of cash equivalents or our ability to meet our financing objectives. Dislocations in the credit market may adversely impact the value and/or liquidity of cash equivalents owned by us.

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

If we are unable to successfully remediate any material weaknesses in our internal control, the accuracy and timing of our financial reporting may be adversely affected, we may be unable to maintain compliance with securities law requirements regarding timely filing of periodic reports in addition to applicable stock exchange listing requirements, investors may lose confidence in our financial reporting, and our stock price may decline as a result. We also could become subject to investigations by Nasdaq, the SEC, or other regulatory authorities.

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

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

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

As of December 31, 2018, we had federal net operating loss carryforwards of $527.3 million, of which $502.6 million will, if not used, expire at various dates through 2037, and federal research and development tax credit carryforwards of $10.9 million, which will, if not used, expire at various dates through 2038. To the extent that they expire unused, these net operating loss and tax credit carryforwards will not be available to offset our future income tax liabilities. Federal net operating losses incurred in 2018 and in future years may be carried forward indefinitely, but the deductibility of such carryforwards is limited to 80% of our taxable income in the year in which such carryforwards are used.

In addition, under Section 382 of the Internal Revenue Code of 1986, as amended, or the Code, and corresponding provisions of state law, if a corporation undergoes an "ownership change," which is generally defined as a greater than 50% change, by value, in its equity ownership over a three-year period, the corporation's ability to use its pre-change net operating loss and credit carryforwards to reduce its tax liability for post-change periods may be limited. We have not determined if we have experienced Section 382 ownership changes in the past and if a portion of our net operating loss and tax credit carryforwards is subject to an annual limitation under Section 382. We also may experience ownership changes in the future as a result of shifts in our stock ownership, some of which may be outside of our control. In addition, we have not conducted a detailed study to document whether our historical activities qualify to support the research and development credits currently claimed as a carryforward. A detailed study could result in adjustment to our research and development credit carryforwards. If we determine that an ownership change has occurred and our ability to use our historical net operating loss and tax credit carryforwards is materially limited, or if our research and development carryforwards are adjusted, our use of those attributes to offset future income tax liabilities would be limited.

The Tax Cuts and Jobs Act of 2017 could adversely affect our business and financial condition.

On December 22, 2017, President Trump signed into law new legislation, commonly referred to as the Tax Cuts and Jobs Act of 2017, or the Act, that significantly revised the Code. The Act contains, among other things, significant changes to corporate taxation, including reduction of the corporate tax rate from a top marginal rate of 35% to a flat rate of 21%, limitation of the tax deduction for interest expense to 30% of adjusted earnings (except for certain small businesses), limitation of the deduction for net operating losses to 80% of current year taxable income and elimination of net operating loss carrybacks, one-time taxation of offshore earnings at reduced rates regardless of whether they are repatriated, elimination of U.S. tax on foreign earnings (subject to certain important exceptions), immediate deductions for certain new investments instead of deductions for depreciation expense over time, and modifying or repealing many business deductions and credits. Notwithstanding the reduction in the corporate income tax rate, the overall impact of the Act is uncertain and our business and financial condition could be adversely affected. In addition, it is uncertain how various states will respond to the Act. The impact of this tax reform on holders of our common stock is also uncertain and could be adverse. We urge our stockholders to consult with their legal and tax advisors with respect to this legislation and the potential tax consequences of investing in or holding our common stock.

ITEM 1B. Unresolved Staff Comments

None.

ITEM 2. Properties

We sublease our principal facilities, which consist of approximately 3,000 square feet of office space located at 1 Broadway, Cambridge, Massachusetts. Our lease arrangement is cancellable with 30 days' notice to our landlord. We believe that our existing facilities are sufficient for our current needs and for the foreseeable future.

ITEM 3. Legal Proceedings

On February 25, 2019, a class action lawsuit was filed against us and certain of our present officers and a former officer, Michael Bailey, Matthew Dallas, and Keith Ehrlich, in the Southern District of New York for the District of New York, captioned *David Hackel v. AVEO Pharmaceuticals, Inc., et al*, No. 1:19-cv-01722-AT. The complaint purports to be brought on behalf of shareholders who purchased our common stock between August 4, 2016 through January 31, 2019. The complaint generally alleges that we and the officers violated Sections 10(b) and/or 20(a) of the Securities Exchange Act of 1934 and Rule 10b-5 promulgated thereunder by making allegedly false and/or misleading statements 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 deny any allegations of wrongdoing and intend to vigorously defend against this lawsuit. However, there is no assurance that we will be successful in our defense or that insurance will be available or adequate to fund any settlement or judgment or the litigation costs of the action. Moreover, we are unable to predict the outcome or reasonably estimate a range of possible loss at this time.

For a discussion of certain legal proceedings against us that are no longer pending, including two class action lawsuits filed against us and certain of our former officers and directors in 2013 and a lawsuit filed against us and our former officers by the SEC in 2016, each alleging that we violated federal securities laws by misleading investors about our efforts to obtain FDA approval for tivozanib, refer to Part II, Item 7 of this report under the headings "Management's Discussion and Analysis of Financial Condition and Results of Operations—Financial Overview—Class Action Settlement and Settlement Warrants" and Note 13 – *"Legal Proceedings"*, in our consolidated financial statements.

ITEM 4. Mine Safety Disclosures

Not applicable.

PART II

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

Market Information

Our common stock is traded on the Nasdaq Capital Market under the symbol "AVEO".

Holders

As of March 8, 2019, there were approximately 43 holders of record of our common stock. We believe that the number of beneficial owners of our common stock at that date was substantially greater.

Dividends

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

Purchase of Equity Securities

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

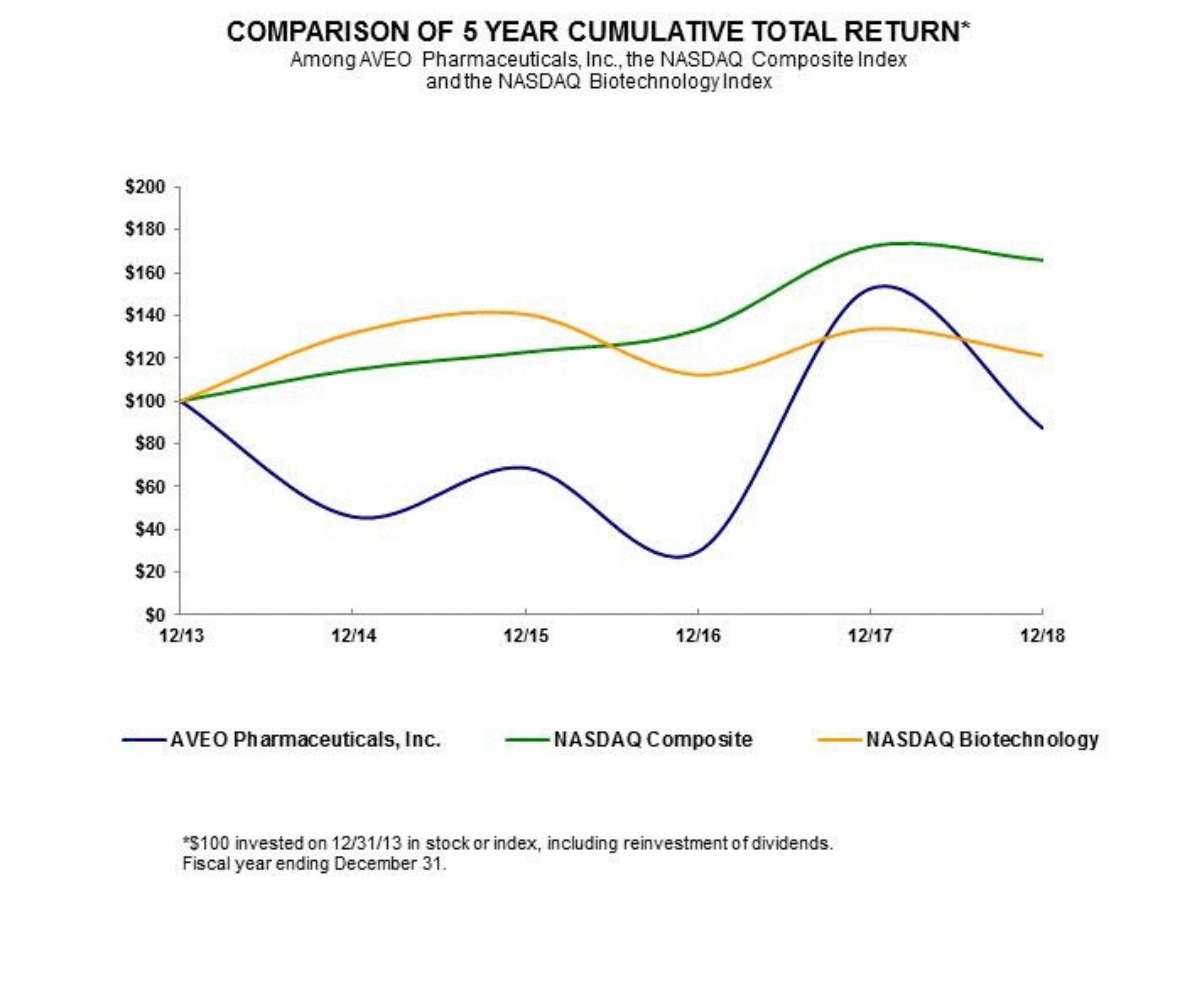
Recent Sales of Unregistered Securities

None.

Comparative Stock Performance Graph

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

The graph below matches AVEO Pharmaceuticals, Inc.'s cumulative 5-Year total shareholder return on common stock with the cumulative total returns of the Nasdaq Composite index and the Nasdaq Biotechnology index. The graph tracks the performance of a $100 investment in our common stock and in each index (with the reinvestment of all dividends) from 12/31/2013 to 12/31/2018.



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

	12/13	12/14	12/15	12/16	12/17	12/18
AVEO Pharmaceuticals, Inc.	**100.00**	**45.91**	**68.85**	**29.51**	**152.46**	**87.43**
Nasdaq Composite	**100.00**	**114.62**	**122.81**	**133.19**	**172.11**	**165.84**
Nasdaq Biotechnology	**100.00**	**131.71**	**140.56**	**112.25**	**133.67**	**121.24**

ITEM 6. Selected Financial Data

The following selected consolidated financial data should be read in conjunction with our Consolidated Financial Statements and the Notes thereto and Management's Discussion and Analysis of Financial Condition and Results of Operations included elsewhere in this Annual Report on Form 10-K. The Balance Sheet Data at December 31, 2018 and 2017 and the Statement of Operations Data for each of the three years in the period ended December 31, 2018 have been derived from our audited Consolidated Financial Statements for such years, included elsewhere in this Annual Report on Form 10-K. The Balance Sheet Data at December 31, 2016, 2015 and 2014, and the Statement of Operations Data for each of the two years in the period ended December 31, 2015 have been derived from the audited Consolidated Financial Statements for such years not included in this Annual Report on Form 10-K.

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

	Years Ended December 31,				
Statement of Operations data:	**2018**	**2017**	**2016**	**2015**	**2014**
	(in thousands, except per share data)				
Revenue	$ 5,409	$ 7,579	$ 2,515	$ 19,024	$ 18,123
Operating expenses:					
Research and development	20,652	25,179	23,703	12,875	38,254
General and administrative	10,781	9,138	8,205	10,217	18,589
Settlement costs	(667)	2,073	—	4,000	—
Restructuring and lease exit	—	—	—	4,358	11,729
Total operating expenses	30,766	36,390	31,908	31,450	68,572
Loss from operations	(25,357)	(28,811)	(29,393)	(12,426)	(50,449)
Interest expense, net	(2,191)	(2,373)	(1,949)	(2,286)	(2,356)
Change in fair value of PIPE Warrant liability	19,919	(33,740)	4,751	—	—
Other income (expense)	2,300	—	(195)	(289)	66
Net loss before income taxes	(5,329)	(64,924)	(26,786)	(15,001)	(52,739)
Provision for income taxes	—	(101)	(101)	—	—
Net loss	$ (5,329)	$ (65,025)	$ (26,887)	$ (15,001)	$ (52,739)
Net loss per share - basic	$ (0.04)	$ (0.61)	$ (0.39)	$ (0.27)	$ (1.01)
Weighted average number of common shares outstanding	120,592	105,930	69,268	55,701	52,289
Net loss per share - diluted	$ (0.19)	$ (0.61)	$ (0.39)	$ (0.27)	$ (1.01)
Weighted average number of common shares and dilutive common share equivalents outstanding	130,731	105,930	69,268	55,701	52,289

	Years Ended December 31,				
Balance sheet data:	**2018**	**2017**	**2016**	**2015**	**2014**
	(in thousands)				
Cash, cash equivalent, and marketable securities	$ 24,427	$ 33,525	$ 23,348	$ 34,135	$ 52,306
Working capital	9,818	18,059	15,966	27,978	18,773
Total assets	27,935	50,198	27,285	40,542	70,662
Loans payable, including current portion, net of discount	19,033	18,477	14,003	9,471	20,652
Accumulated deficit	(595,009)	(586,969)	(521,916)	(495,029)	(480,028)
Total stockholders' (deficit) equity	(27,227)	(40,763)	(1,923)	17,227	20,606

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

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

Overview

We are a biopharmaceutical company 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 "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.

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.

Strategic Partnerships

AstraZeneca

In December 2018, we entered into a clinical supply agreement, or the AstraZeneca 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. We did not incur any costs under the AstraZeneca Agreement in the year ended December 31, 2018.

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 China National Drug Administration, or 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 approvals 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 a license agreement with Novartis, or 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 change in strategic direction at Novartis. Effective August 28, 2018, the Novartis License Agreement was terminated, and we regained the 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 an agreement with Novartis, or 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 the AV-380 program as well as cooperation regarding our future regulatory filings relating to AV-380. Novartis is also required to provide the AV-380 drug supply, valued at approximately $4.0 million, to us at no charge. Pursuant to the AV-380 Transfer Agreement, Novartis made a one-time payment to us of $2.3 million in January 2019, which 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 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.

In connection with the AV-380 Transfer Agreement, the $2.3 million payment obligation due from Novartis was not considered a revenue transaction due to the effective termination of the Novartis Agreement on August 28, 2018 and was instead considered other income. We evaluated the return of the AV-380 drug supply, valued at approximately $4.0 million, and determined that the inventory was not capitalizable as future economic benefit is not probable at this time due to the AV-380 drug candidate being in the pre-clinical development stage.

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 related to the sale of AV-203, up to 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 did not owe KHK another milestone payment in connection with the dosing of the first patient in our TIVO-3 trial and would not owe a milestone payment to KHK when we file our anticipated NDA with the FDA following the receipt of positive TIVO-3 topline data. 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 in September 2017 upon the receipt of marketing authorization from the European Commission for tivozanib (FOTIVDA) and the $2.0 million 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 in November 2018 upon EUSA's reimbursement approval for FOTIVDA as a first-line treatment for RCC 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.

Financial Overview

We do not have a history of being profitable and, as of December 31, 2018, we had an accumulated deficit of $595.0 million. We anticipate that we will continue to incur significant operating costs over the next several years as we continue our planned development activities for our preclinical and clinical products. We will need additional funding to support our operating activities, and the timing and nature of activities contemplated for 2019 and thereafter will be conducted subject to the availability of sufficient financial resources. Refer to the "—Going Concern" and "Liquidity and Capital Resources—Liquidity and Going Concern" sections for a further discussion of our funding requirements.

Revenue

On January 1, 2018, we adopted the provisions of Accounting Standards Codification Topic 606, *Revenue From Contracts with Customers*, or ASC 606. Refer to Note 3, "*Significant Accounting Policies - Revenue Recognition"* and Note 4, *"Collaborations and License Agreements*", to our consolidated financial statements included elsewhere in this Annual Form 10-K for further information.

Our revenues have historically been generated primarily through collaborative research, development and commercialization agreements. Payments to us under these arrangements typically include one or more of the following: non-refundable, upfront license fees; option exercise fees; funding of research and/or development efforts; milestone payments; and royalties on future product sales. In November 2017, we began earning sales royalties upon EUSA's commencement of the first commercial launch of tivozanib (FOTIVDA).

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

Research and Development Expenses

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

- employee-related expenses, including salaries, bonuses, benefits and stock-based compensation expense;
- external development-related expenses, including clinical trials conducted by contract research organizations and investigative sites, preclinical studies and consultants;
- the cost of acquiring and manufacturing drug development related materials and related distribution;
- costs associated with outsourced development activities, including regulatory and medical affairs;
- sublicense fees for, and milestone payments related to, in-licensed products and technology; and
- facilities, depreciation and other allocated expenses, which include direct and allocated expenses for rent and maintenance of facilities and equipment, and depreciation of fixed assets.

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

We anticipate that research and development expenses will continue to decrease during 2019 as we seek to complete the TIVO-3 and TiNivo trials, partially offset by an increase in connection with the planned commencement in 2019 of a phase 1/2 study of tivozanib in combination with IMFINZI (durvalumab) in advanced, unresectable HCC in collaboration with AstraZeneca. This estimate excludes possible additional clinical trials we may sponsor and any related drug manufacturing and drug supply distribution, and pre-commercialization activities that we may undertake subject to our decision whether to submit an NDA for tivozanib to the FDA following the availability of more mature OS results and subject to the availability of sufficient financial resources.

Currently, we track direct external development expenses and direct salary on a program-by-program basis and allocate general-related expenses, such as indirect compensation, benefits and consulting fees, to each program based on the personnel resources allocated to such program. Facilities, IT costs and stock-based compensation are not allocated amongst programs and are considered overhead.

Uncertainties of Estimates Related to Research and Development Expenses

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

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

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

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

General and Administrative Expenses

General and administrative expenses consist principally of salaries, bonuses and related costs for personnel in executive, finance, corporate development, information technology, legal and human resource functions. Other general and administrative expenses include facility costs not otherwise included in research and development expenses, patent filing, prosecution and defense costs and professional fees for legal, consulting, auditing and tax services. We anticipate that our general and administrative expenses will remain at current levels during 2019, excluding pre-commercialization activities that we may undertake subject to our decision whether to submit an NDA for tivozanib to the FDA following the availability of more mature OS results and subject to the availability of sufficient financial resources.

Interest Expense, Net

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

Income Taxes

We recorded a loss for the years ended December 31, 2018, 2017, and 2016, and since we maintain a full valuation allowance on all of our deferred tax assets, we have recorded no income tax provision or benefit during the years ended December 31, 2018, 2017, and 2016, except for a $0.1 million provision recorded in each of the years ended December 31, 2017 and 2016 related to withholding taxes incurred in a foreign jurisdiction.

On December 22, 2017, President Trump signed into law legislation commonly known as the Tax Cuts and Jobs Act, or the Act. The Act, among other things, contains significant changes to corporate taxation, including reduction of the corporate tax rate from a top marginal rate of 35% to a flat rate of 21%, limitation of the tax deduction for interest expense to 30% of adjusted earnings (except for certain small businesses), limitation of the deduction for net operating losses to 80% of current year taxable income and elimination of net operating loss carrybacks, one time taxation of offshore earnings at reduced rates regardless of whether they are repatriated, elimination of U.S. tax on foreign earnings (subject to certain important exceptions), immediate deductions for certain new investments instead of deductions for depreciation expense over time, and modifying or repealing many business deductions and credits.

Significant Accounting Policies and Significant Judgments and Estimates

Our discussion and analysis of our financial condition and results of operations are based on our consolidated financial statements and the notes thereto included elsewhere in this Annual Report on Form 10-K, which have been prepared in accordance with accounting principles generally accepted in the United States. The preparation of these financial statements requires us to make estimates and judgments that affect the reported amounts of assets and liabilities, the disclosure of contingent assets and liabilities at the date of the financial statements, and the reported amounts of revenues and expenses during the reported periods. On an ongoing basis, we evaluate our estimates and judgments for changes in facts and circumstances, including those related to revenue recognition, contract research accruals, measurements of the PIPE Warrants liability and estimated Settlement Liability, and stock-based compensation. We base our estimates on historical experience and various other assumptions that we believe to be reasonable under the circumstances. Material changes in these estimates could occur in the future. Changes in estimates are recorded in the period in which they become known. Actual results may differ from our estimates if past experience or other assumptions do not turn out to be substantially accurate. During the year ended December 31, 2018, there were no material changes to our critical accounting policies as reported in our Annual Report on Form 10-K for the year ended December 31, 2017, which we filed with the SEC on March 13, 2018, except as set forth below:

On January 1, 2018, we adopted ASC 606 using the modified retrospective method and applied the new guidance to the most current period presented with the cumulative effect of changes reflected in the opening balance of the accumulated deficit. The adoption of ASC 606 resulted in an approximate $2.7 million increase in each of deferred revenue and the accumulated deficit at the transition date. The transition adjustment related solely to our EUSA Agreement. The transition adjustment resulted from a change to our accounting policy with respect to the recognition of milestone payments as a result of adopting ASC 606. Refer to Note 3 – "*Significant Accounting Policies - Revenue Recognition"* and Note 4 – *"Collaborations and License Agreements – EUSA*", to our consolidated financial statements included elsewhere in this Annual Form 10-K for further information.

Revenue Recognition

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

Collaboration Arrangements Within the Scope of ASC 808, Collaborative Arrangements

We analyze our collaboration arrangements to assess whether such arrangements involve joint operating activities performed by parties that are both active participants in the activities and exposed to significant risks and rewards dependent on the commercial success of such activities and are therefore within the scope of ASC Topic 808, *Collaborative Arrangements* ("ASC 808"). This assessment is performed throughout the life of the arrangement based on changes in the responsibilities of all parties in the arrangement. For collaboration arrangements that are deemed to be within the scope of ASC 808, we first determine which elements of the collaboration are deemed to be within the scope of ASC 808 and those that are more reflective of a vendor-customer relationship and therefore within the scope of ASC 606, *Revenue from Contracts with Customers* ("ASC 606"). Our policy is generally to recognize amounts received from collaborators in connection with joint operating activities that are within the scope of ASC 808 as a reduction in research and development expense.

Arrangements Within the Scope of ASC 606, Revenue from Contracts with Customers

Effective January 1, 2018, we adopted ASC 606 using the modified retrospective transition method. Under this method, we have recognized the cumulative effect of the adoption as an adjustment to the opening balance of accumulated deficit in the current period consolidated balance sheet. Financial results for the year ended December 31, 2018, are presented under ASC 606, while prior period amounts are not adjusted and continue to be reported in accordance with our historical accounting under ASC 605, *Revenue Recognition*. ASC 606 applies to all contracts with customers, except for contracts that are within the scope of other standards, such as collaboration arrangements and leases.

Under ASC 606, we recognize revenue when our customers obtain control of promised goods or services, in an amount that reflects the consideration which we determine we expect to receive in exchange for those goods or services. To determine revenue recognition for arrangements that we determine are within the scope of ASC 606, we perform the following five steps: (i) identify the contract(s) with a customer; (ii) identify the performance obligation(s) in the contract; (iii) determine the transaction price; (iv) allocate the transaction price to the performance obligation(s) in the contract; and (v) recognize revenue when (or as) we satisfy our performance obligation(s). As part of the accounting for these arrangements, we must make significant judgments, including identifying performance obligations in the contract, estimating the amount of variable consideration to include in the transaction price and allocating the transaction price to each performance obligation.

Once a contract is determined to be within the scope of ASC 606, we assess the goods or services promised within the contract and determine those that are performance obligations. Arrangements that include rights to additional goods or services that are exercisable at a customer's discretion are generally considered options. We assess if these options provide a material right to the customer and if so, they are considered performance obligations. The exercise of a material right is accounted for as a contract modification for accounting purposes.

We assess whether each promised good or service is distinct for the purpose of identifying the performance obligations in the contract. This assessment involves subjective determinations and requires management to make judgments about the individual promised goods or services and whether such are separable from the other aspects of the contractual relationship. Promised goods and services are considered distinct provided that: (i) the customer can benefit from the good or service either on its own or together with other resources that are readily available to the customer (that is, the good or service is capable of being distinct) and (ii) the entity's promise to transfer the good or service to the customer is separately identifiable from other promises in the contract (that is, the promise to transfer the good or service is distinct within the context of the contract). In assessing whether a promised good or service is distinct, we consider factors such as the research, manufacturing and commercialization capabilities of the collaboration partner and the availability of the associated expertise in the general marketplace. We also consider the intended benefit of the contract in assessing whether a promised good or service is separately identifiable from other promises in the contract. If a promised good or service is not distinct, an entity is required to combine that good or service with other promised goods or services until it identifies a bundle of goods or services that is distinct.

The transaction price is then determined and allocated to the identified performance obligations in proportion to their standalone selling prices, or SSP, on a relative SSP basis. SSP is determined at contract inception and is not updated to reflect changes between contract inception and when the performance obligations are satisfied. Determining the SSP for performance obligations requires significant judgment. In developing the SSP for a performance obligation, we consider applicable market conditions and relevant entity-specific factors, including factors that were contemplated in negotiating the agreement with the customer and estimated costs. We validate the SSP for performance obligations by evaluating whether changes in the key assumptions used to determine the SSP will have a significant effect on the allocation of arrangement consideration between multiple performance obligations.

If the consideration promised in a contract includes a variable amount, we estimate the amount of consideration to which it will be entitled in exchange for transferring the promised goods or services to a customer. We determine the amount of variable consideration by using the expected value method or the most likely amount method. We include the unconstrained amount of estimated variable consideration in the transaction price. The amount included in the transaction price is constrained to the amount for which it is probable that a significant reversal of cumulative revenue recognized will not occur. At the end of each subsequent reporting period, we re-evaluate the estimated variable consideration included in the transaction price and any related constraint, and if necessary, adjust our estimate of the overall transaction price. Any such adjustments are recorded on a cumulative catch-up basis in the period of adjustment.

In determining the transaction price, we adjust consideration for the effects of the time value of money if the timing of payments provides us with a significant benefit of financing. We do not assess whether a contract has a significant financing component if the expectation at contract inception is such that the period between payment by the licensees and the transfer of the promised goods or services to the licensees will be one year or less. We assess each of its revenue generating arrangements in order to determine whether a significant financing component exists and concluded that a significant financing component does not exist in any of our arrangements.

We then recognize as revenue the amount of the transaction price that is allocated to the respective performance obligation when (or as) each performance obligation is satisfied at a point in time or over time, and if over time based on the use of an output or input method.

Licenses of intellectual property: The terms of our license agreements include the license of functional intellectual property, given the functionality of the intellectual property is not expected to change substantially as a result of our ongoing activities. If the license to our intellectual property is determined to be distinct from the other performance obligations identified in the arrangement, we recognize revenues from the portion of the transaction price allocated to the license when the license is transferred to the licensee and the licensee is able to use and benefit from the license. For licenses that are bundled with other promises (that is, for licenses that are not distinct from other promised goods and services in an arrangement), we utilize judgment to assess the nature of the combined performance obligation to determine whether the combined performance obligation is satisfied over time or at a point in time and, if over time, the appropriate method of measuring progress for purposes of recognizing revenue. We evaluate the measure of progress each reporting period and, if necessary, adjusts the measure of performance and related revenue recognition.

Research and development funding: Arrangements that include payment for research and development services are generally considered to have variable consideration. If and when we assess the payment for these services is no longer subject to the constraint on variable consideration, the related revenue is included in the transaction price.

Milestone payments: At the inception of each arrangement that includes non-refundable payments for contingent milestones, including preclinical research and development, clinical development and regulatory, we evaluate whether the milestones are considered probable of being achieved and estimate the amount to be included in the transaction price using the most likely amount method. If it is probable that a significant revenue reversal would not occur, the associated milestone value is included in the transaction price. Milestone payments that are not within the control of us or the licensee, such as regulatory approvals, are not considered probable of being achieved until those approvals are received. At the end of each reporting period, we re-evaluate the probability of the achievement of contingent milestones and the likelihood of a significant reversal of such milestone revenue, and if necessary, adjust our estimate of the overall transaction price. Any such adjustments are recorded on a cumulative catch-up basis, which would affect collaboration and licensing revenue in the period of adjustment. This quarterly assessment may result in the recognition of revenue related to a contingent milestone payment before the milestone event has been achieved.

Royalties: For arrangements that include sales-based royalties, including milestone payments based on the level of sales, and the license is deemed to be the predominant item to which the royalties relate, we recognize revenue at the later of (i) when the related sales occur, or (ii) when the performance obligation to which some or all of the royalty has been allocated has been satisfied (or partially satisfied).

The following table summarizes the total revenues earned in the years ended December 31, 2018, 2017 and 2016, respectively, by partner (in thousands). Refer to Note 4 *"Collaborations and License Agreements"* of the notes to our consolidated financial statements included elsewhere in this Annual Report on Form 10-K regarding specific details.

	Years Ended December 31,		
	2018	2017	2016
Strategic Partner:	($ in thousands)		
EUSA	$ 3,409	$ 4,414	$ 395
CANbridge	2,000	1,000	1,028
Novartis	—	1,800	—
Biogen Idec	—	—	38
Pharmstandard	—	—	939
Ophthotech	—	115	115
Other	—	250	—
Total revenues	$ 5,409	$ 7,579	$ 2,515

Accrued Expenses and Accrued Clinical Trial Costs and Contract Research Liabilities

As part of the process of preparing our financial statements, we are required to estimate accrued expenses. This process involves identifying services which have been performed on our behalf, and estimating the level of service performed and the associated cost incurred for such service as of each balance sheet date in our financial statements. Given our current business, the primary area of uncertainty concerning accruals which could have a material effect on our operating results is with respect to service fees paid to contract manufacturers in conjunction with the production of clinical drug supplies and to contract research organizations in connection with our clinical trials. In connection with all of the foregoing service fees, our estimates are most affected by our understanding of the status and timing of services provided. The majority of our service providers, including contract research organizations, invoice us in arrears for services performed. In the event that we do not identify some costs which have begun to be incurred, or we under or overestimate the level of services performed or the costs of such services in a given period, our reported expenses for such period would be understated or overstated. We currently reflect the effects of any changes in estimates based on changes in facts and circumstances directly in our operations in the period such change becomes known.

Our arrangements with contract research organizations in connection with clinical trials often provide for payment prior to commencing the project or based upon predetermined milestones throughout the period during which services are expected to be performed. We recognize expense relating to these arrangements based on the various services provided over the estimated time to completion. The date on which services commence, the level of services performed on or before a given date, and the cost of such services are often determined based on subjective judgments. We make these judgments based upon the facts and circumstances known to us based on the terms of the contract and our ongoing monitoring of service performance. During the years ended December 31, 2018, 2017 and 2016, we had arrangements with multiple contract research organizations whereby these organizations commit to performing services for us over multiple reporting periods. We recognize the expenses associated with these arrangements based on our expectation of the timing of the performance of components under these arrangements by these organizations. Generally, these components consist of the costs of setting up the trial, monitoring the trial, closing the trial and preparing the resulting data. Costs related to patient enrollment in clinical trials are accrued as patients are enrolled in the trial.

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

Stock-Based Compensation

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

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

We use the Black-Scholes option pricing model to value our stock option awards without market conditions, which requires us to make certain assumptions regarding the expected volatility of our common stock price, the expected term of the option grants, the risk-free interest rate and the dividend yield with respect to our common stock. We calculate volatility using our historical stock price data. Due to the lack of our own historical data, we elected to use the "simplified" method for "plain vanilla" options to estimate the expected term of our stock option grants. Under this approach, the weighted-average expected life is presumed to be the average of the vesting term and the contractual term of the option. The risk-free interest rate used for each grant is based on the U.S. Treasury yield curve in effect at the time of grant for instruments with a similar expected life. We utilize a dividend yield of zero based on the fact that we have never paid cash dividends and have no present intention to pay cash dividends.

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

During the years ended December 31, 2018, 2017 and 2016, respectively, the assumptions used in the Black-Scholes pricing model for new grants were as follows:

	Years Ended December 31,		
	2018	2017	2016
Volatility factor	80.18% - 83.61%	71.82% - 80.15%	72.18% - 74.47%
Expected term (in years)	5.50 - 6.25	5.50 - 6.25	3.00 - 6.25
Risk-free interest rates	2.64% - 3.10%	1.84% - 2.22%	1.07% - 2.01%
Dividend yield	—	—	—

On January 1, 2017, we adopted ASU No. 2016-09, *Compensation–Stock Compensation (Topic 718): Improvements to Employee Share-Based Payment Accounting* and elected to account for forfeitures as they occur. Prior to 2017, we included an estimate of the value of the awards that would be forfeited in calculating compensation costs, which we estimated based upon actual historical forfeitures.

We recognized stock-based compensation expense of approximately $2.5 million, $1.1 million and $1.0 million for the years ended December 31, 2018, 2017, and 2016, respectively. As of December 31, 2018, we had approximately $5.8 million of total unrecognized stock-based compensation expense for stock options, which we expect to recognize over a weighted-average period of approximately 2.5 years.

We record compensation expense only for those awards that ultimately vest.

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

Warrants Issued in Connection with Private Placement

In May 2016, we issued warrants to purchase an aggregate of 17,642,482 shares of our common stock in connection with a private placement financing, which we refer to herein as the PIPE Warrants. Refer to"—Liquidity and Capital Resources—Private Placement/PIPE Warrants" below and Note 3, "*Significant Accounting Policies - Warrants Issued in Connection with Private Placement*" to our consolidated financial statements included elsewhere in this Annual Report on Form 10-K, for a further discussion.

The PIPE Warrants are subject to revaluation at each balance sheet date, and any changes in fair value are recorded as a non-cash gain or (loss) in the Statement of Operations as a component of other income (expense), net until the earlier of their exercise or expiration or upon the completion of a liquidation event. Upon exercise, the PIPE Warrants are subject to revaluation just prior to the date of exercise and any changes in fair value are recorded as a non-cash gain or (loss) in the Statement of Operations as a component of other income (expense), net and the corresponding reduction in the warrant liability is recorded as additional paid-in capital in the Balance Sheet as a component of stockholder's equity.

As of December 31, 2018, PIPE Warrants exercisable for 803,108 shares of common stock had been exercised, for cash proceeds of approximately $0.8 million, and PIPE Warrants exercisable for 16,839,375 shares of common stock were outstanding. In July 2017, we issued to Hercules Capital Inc., or Hercules, 259,067 shares of common stock upon its exercise of all of its PIPE Warrants, and we received approximately $0.3 million in cash proceeds. In 2018, PIPE Warrants with respect to 544,041 shares of common stock underlying such PIPE Warrants were exercised, and we issued 544,041 shares of our common stock and received approximately $0.5 million in cash proceeds.

We recorded a non-cash gain of approximately $19.9 million in the year ended December 31, 2018, a non-cash loss of $33.7 million in the year ended December 31, 2017 and a non-cash gain of approximately $4.8 million in the year ended December 31, 2016 in our Statement of Operations attributable to the increases and decreases in the fair value of the warrant liability that resulted from lower stock prices as of December 31, 2018, higher stock prices as of December 31, 2017 and lower stock prices as of December 31, 2016, relative to prior periods. We recorded a reduction in the warrant liability attributable to warrant exercises, with a corresponding increase to additional paid-in capital, of approximately $1.2 million, $0.6 million and $0 in the years ended December 31, 2018, 2017 and 2016, respectively.

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

	Original Issuance	December 31, 2016	December 31, 2017	December 31, 2018
Expected price volatility	76.25%	78.18%	84.86%	82.64%
Expected term (in years)	5.00	4.50	3.50	2.50
Risk-free interest rates	1.22%	1.93%	2.09%	2.47%
Stock price	$ 0.89	$ 0.54	$ 2.79	$ 1.60
Dividend yield	—	—	—	—

Prior Class Action Settlement and Settlement Warrants

In December 2017, we entered into a binding memorandum of understanding, or MOU, to settle a securities class action lawsuit, or the Class Action, captioned *In re AVEO Pharmaceuticals, Inc. Securities Litigation et al.*, No. 1:13-cv-11157-DJC, filed in 2013 in the United States District Court for the District of Massachusetts, or the District Court, against us and certain of our former officers. The Class Action was purportedly brought on behalf of stockholders who purchased our common stock between May 16, 2012 and May 1, 2013, or the Class.

Upon entry into the MOU, our liability related to this settlement became estimable and probable. Accordingly, we recorded an estimated $17.1 million contingent liability, including (a) $15.0 million for the cash portion of the settlement with a corresponding insurance recovery for the 100% portion to be paid directly by certain of our insurance carriers, and (b) an approximate $2.1 million estimate for the fair value on December 31, 2017 of 2.0 million warrants to purchase shares of our common stock, or the Settlement Warrants, that we agreed to issue to the Class, with a corresponding non-cash charge to the Statement of Operations as a component of operating expenses. The Settlement Warrants are exercisable for a one-year period from their date of issue at an exercise price equal to $3.00 per share, which was the closing price on December 22, 2017, the trading day prior to the execution of the MOU.

In January 2018, we entered into a definitive stipulation of settlement agreement, or the Stipulation. In February 2018, the District Court preliminarily approved the Stipulation, following which the insurance carriers funded the settlement escrow account related to the $15.0 million cash portion of the settlement. On May 30, 2018, the District Court approved the Stipulation in its order of final approval and final judgment, or the Final Judgment.

The settlement became effective on June 29, 2018, or the Effective Date, which was the date on which all of the following conditions had been met: (a) a Final Judgment containing the requisite release of claims had been entered by the District Court; (b) no appeal was pending with respect to the Final Judgment; (c) the Final Judgment had not been reversed, modified, vacated or amended; (d) the time to file any appeal from the Final Judgment had expired without the filing of an appeal or an order dismissing the appeal or affirming the Final Judgment had been entered, and any time to file a further appeal (including a writ of certiorari or for reconsideration of the appeal) had expired; and (e) the MOU and any settlement agreement with respect to the claims released in the Final Judgment had not expired or been terminated. Pursuant to the Final Judgment, all claims against us were released upon the Effective Date. In addition, pursuant to the Stipulation, we had no interest in the settlement escrow account subsequent to the Effective Date. Accordingly, the $15.0 million contingent liability associated with the cash portion of the settlement and the corresponding insurance recovery were eliminated on the Effective Date. We had agreed to use our best efforts to issue and deliver the Settlement Warrants within ten business days following the Effective Date. On July 16, 2018, we issued and delivered the Settlement Warrants in accordance with the Stipulation and filed a corresponding shelf registration statement to register the shares of common stock underlying the Settlement Warrants which was declared effective by the SEC on July 25, 2018.

The estimated fair value of the Settlement Warrants was determined using the Black-Scholes pricing model. The estimated fair value of the Settlement Warrants was subject to revaluation at each balance sheet date and any changes in fair value were recorded as a non-cash gain or (loss) in the Statement of Operations as a component of operating expenses until the Settlement Warrants were issued. We recorded a non-cash gain of approximately $0.7 million in the year ended December 31, 2018 in our Statement of Operations attributable to the decrease in the fair value of the Settlement Warrants from December 31, 2017 to the date the Settlement Warrants were issued. In July 2018, upon the issuance of the Settlement Warrants, we reclassified the approximate $1.4 million value of the Settlement Warrants from a liability to stockholders equity as a component of additional paid-in capital based upon the terms of the warrant agreement and, accordingly, the approximate $1.4 million contingent liability on our balance sheet associated with the warrant portion of the settlement was eliminated.

Refer to Note 13, "*Legal Proceedings*" *to* our consolidated financial statements and Part I, Item 3 under the heading "Legal Proceedings" included elsewhere in this Annual Report on Form 10-K, for a further discussion of the Class Action settlement.

The key assumptions used to estimate the fair value of the Settlement Warrants were as follows:

	December 31, 2017	June 30, 2018
Expected price volatility	101.52%	62.74%
Expected term (in years)	1.00	1.00
Risk-free interest rates	1.76%	2.37%
Stock price	$ 2.79	$ 2.90
Dividend yield	—	—

Results of Operations

Comparison of Years Ended December 31, 2018, 2017 and 2016

Revenues

	Years Ended December 31,			2018 / 2017 Comparison		2017 / 2016 Comparison	
	2018	2017	2016	$	%	$	%
Strategic Partner:	($ in thousands)						
EUSA	$ 3,409	$ 4,414	$ 395	$(1,005)	(23)%	$4,019	1017%
CANbridge	2,000	1,000	1,028	1,000	100%	(28)	(3)%
Novartis	—	1,800	—	(1,800)	(100)%	1,800	100%
Biogen Idec	—	—	38	—	—%	(38)	(100)%
Pharmstandard	—	—	939	—	—%	(939)	(100)%
Ophthotech	—	115	115	(115)	(100)%	—	—%
Other	—	250	—	(250)	(100)%	250	100%
Total revenues	$ 5,409	$ 7,579	$ 2,515	$(2,170)	(29)%	$5,064	201%

In 2018 as compared to 2017, revenue decreased under our partnership with EUSA by $1.0 million due primarily to a change in our accounting policy with respect to milestone payments as a result of the adoption of ASC 606 on January 1, 2018.

Previously, under ASC 605, we recognized regulatory milestones when they were achieved. Under ASC 606, milestone payments are included in the transaction price when they are no longer subject to the variable consideration constraint and, to the extent the milestone payment corresponds to a performance obligation where revenue is recognized over time, the milestone payment is recognized over the performance period.

The $4.0 million research and development reimbursement payment upon marketing approval by the European Commission in RCC in August 2017 was recognized as revenue in the third quarter of 2017 in accordance with ASC 605-28, *Revenue Recognition—Milestone Method*. The impact of the adoption of ASC 606 on January 1, 2018 resulted in increases of approximately $2.7 million in each of deferred revenue and the accumulated deficit. This amount represents the portion of the $4.0 million research and development reimbursement payment for marketing approval by the European Commission in RCC that will be recognized over the remainder of our performance period through 2022 pursuant to the provisions of ASC 606.

In February 2018, EUSA obtained reimbursement approval for tivozanib (FOTIVDA) from the NICE in the United Kingdom in first-line RCC and, accordingly, we earned a $2.0 million milestone payment from EUSA. In accordance with ASC 606, we recognized approximately $0.7 million of this milestone payment in revenue for the cumulative catch-up for the period from contract execution in December 2015 through the milestone achievement in February 2018, with the approximate $1.3 million balance classified as deferred revenue that is being recognized as revenue over the remainder of our performance period through April 2022.

In November 2018, EUSA obtained reimbursement approval for tivozanib (FOTIVDA) from the GKV-SV in Germany in first-line RCC and, accordingly, we earned a $2.0 million milestone payment from EUSA. In accordance with ASC 606, we recognized approximately $0.9 million of this milestone payment in revenue for the cumulative catch-up for the period from contract execution in December 2015 through the milestone achievement in November 2018, with the approximate $1.1 million balance classified as deferred revenue that is being recognized as revenue over the remainder of our performance period through April 2022.

Refer to Note 4 *"Collaborations and License Agreements* – EUSA", to our consolidated financial statements included elsewhere in this Annual Form 10-K, regarding the specific application of ASC 606 to our EUSA Agreement. Refer to Note 3 *"Significant Accounting Policies – Recently Adopted Accounting Pronouncements*", to our consolidated financial statements included elsewhere in this Annual Form 10-K, for a comparison of revenue recognized during the year ended December 31, 2018 under ASC 606 compared to the revenue that would have been recognized in that period had we continued to apply the provisions of ASC 605.

In 2018 as compared to 2017, revenue increased by $1.0 million under our partnership with CANbridge. In August 2018, CANbridge obtained regulatory approval from the CNDA of an IND application for a clinical study of AV-203 in ESCC and, accordingly, we earned a $2.0 million development and regulatory milestone payment. Also, CANbridge agreed to reimburse us $1.0 million for certain manufacturing costs and expenses incurred by us prior to the effective date of the CANbridge agreement with respect to AV-203. CANbridge paid this manufacturing reimbursement in two installments of $0.5 million each, including one in March 2017 and one in September 2017. The timing and amount of revenue recognition for the payments received from CANbridge are the same under ASC 605 and ASC 606.

In 2018 as compared to 2017, revenue decreased by $1.8 million under our former partnership with Novartis. In February 2017, Novartis paid $1.8 million out of its then future payment obligations to us under the former license agreement. The funds were used to satisfy a $1.8 million time-based milestone obligation that we owed to St. Vincent's on March 2, 2017.

In 2017 as compared to 2016, revenue increased by $5.1 million, principally due to a $4.0 million research and development reimbursement payment by EUSA upon the EMA approval of tivozanib (FOTIVDA) in RCC and a $1.8 million milestone payment by Novartis related to AV-380, partially offset by $0.8 million related to the acceleration of deferred revenue that was recognized upon the effective termination of our licensing agreement with Pharmstandard in September 2016.

Research and Development Expenses

	Years Ended December 31,			2018 / 2017 Comparison		2017 / 2016 Comparison	
	2018	2017	2016	$	%	$	%
	($ in thousands)						
Tivozanib	$ 18,249	$ 21,594	$ 21,231	$(3,345)	(15)%	$ 363	2%
AV-380 Program in Cachexia	—	1,850	464	(1,850)	(100)%	1,386	299%
Ficlatuzumab	586	587	746	(1)	(0)%	(159)	(21)%
AV-203	670	—	76	670	100%	(76)	(100)%
Other pipeline programs	—	156	—	(156)	(100)%	156	100%
Overhead	1,147	992	1,186	155	16%	(194)	(16)%
Total research and development expenses	$ 20,652	$ 25,179	$ 23,703	$(4,527)	(18)%	$1,476	6%

In 2018 as compared to 2017, research and development expenses decreased by $4.5 million, principally due to decreases of $3.3 million in net tivozanib expenses and $1.8 million in AV-380 for a time-based milestone obligation due to St. Vincent's in the first quarter of 2017 that was not incurred in 2018, partially offset by the $0.7 million sublicense fee due to Biogen in connection with the $2.0 million development and regulatory milestone we earned under the CANbridge Agreement for regulatory approval from the CNDA of an IND application for a clinical study of AV-203 in ESCC.

The $3.3 million net decrease in tivozanib expenses principally included decreases of $6.5 million for expenses related to the year-to-year conduct of the TIVO-3 and TiNivo trials that completed enrollment in 2017 and $0.8 million for expenses related to pre-commercial manufacturing, partially offset by increases of $2.4 million for expenses related to the preparation of a possible NDA submission and $1.2 million in sublicense fees due to KHK in connection with the $2.0 million milestones we earned under our EUSA Agreement in each of February 2018 and November 2018 for reimbursement approvals in the United Kingdom and Germany, respectively, for the first line treatment of RCC. We initiated the TIVO-3 trial in May 2016 and completed enrollment in August 2017. In 2018 as compared to 2017, the majority of the patients were off treatment in the TIVO-3 trial compared to the trial being in active enrollment in the same period in 2017. We initiated the TiNivo trial in March 2017 and completed enrollment in December 2017.

We anticipate that research and development expenses will continue to decrease during 2019 as we seek to complete the TIVO-3 and TiNivo trials, partially offset by an increase in connection with the planned commencement in 2019 of a phase 1/2 study of tivozanib in combination with IMFINZI (durvalumab) in advanced, unresectable HCC in collaboration with AstraZeneca. This estimate excludes possible additional clinical trials we may sponsor and any related drug manufacturing and drug supply distribution, and pre-commercialization activities that we may undertake subject to our decision whether to submit an NDA for tivozanib to the FDA following the availability of more mature OS results and subject to the availability of sufficient financial resources.

In 2017 as compared to 2016, research and development expenses increased by $1.5 million principally due to a $0.4 million net increase in tivozanib expenses, primarily related to the advancement of the TIVO-3 and TiNivo trials, and a $1.4 million increase in AV-380 expense, primarily related to the net increase in milestone payments due to St. Vincent's under our in-licensing agreement. These increases were partially offset by $0.2 million in lower ficlatuzumab expenses, primarily related to the discontinuation of the FOCAL trial in October 2016.

In 2017 as compared to 2016, the $0.4 million net increase in tivozanib expenses included an increase of $1.3 million, primarily related to the advancement of the TIVO-3 and TiNivo trials, partially offset by a $0.9 million reduction related to cost sharing provided by EUSA in connection with the TiNivo trial. In September 2017, EUSA elected to opt-in to co-develop the ongoing TiNivo trial and made a research and development reimbursement payment to us of $2.0 million that 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. In 2017, we recognized an approximate $0.9 million reduction in research and development expenses related to EUSA's approximate 50% share of the cumulative study-to-date costs incurred as of December 31, 2017 as the TiNivo trial was ongoing at the time EUSA made its opt-in election and EUSA paid the $2.0 million maximum amount of cost sharing per the license agreement in advance. The remaining $1.1 million in prepaid cost sharing was classified as deferred research and development reimbursements as of December 31, 2017 and is being recognized as a reduction in research and development expenses as the related TiNivo trial costs are incurred over the duration of the trial.

In 2017 as compared to 2016, the $1.4 million increase in AV-380 expense is principally due to $1.8 million in research and development expense that was recognized in the first quarter of 2017 in connection with a time-based milestone obligation due to St. Vincent's. In the first quarter of 2016, we recognized approximately $0.4 million in research and development expense in connection with a milestone obligation due to St. Vincent's related to the selection of a development candidate.

General and Administrative Expenses

	Years Ended December 31,			2018 / 2017 Comparison		2017 / 2016 Comparison	
	2018	2017	2016	$	%	$	%
	($ in thousands)						
General and administrative	$ 10,781	$ 9,138	$ 8,205	$1,643	18%	$ 933	11%

In 2018 as compared to 2017, general and administrative expenses increased by $1.6 million, principally due to increases of $0.5 million in professional fees and $1.0 million in non-cash stock-based compensation expense resulting from a higher stock price in 2018 as compared to 2017 in connection with annual stock option grants.

We anticipate that our general and administrative expenses will remain at current levels during 2019, excluding pre-commercialization activities that we may undertake subject to our decision whether to submit an NDA for tivozanib to the FDA following the availability of more mature OS results and subject to the availability of sufficient financial resources.

In 2017 as compared to 2016, general and administrative expenses increased by $0.9 million, principally due to an increase of $0.8 million in professional fees, including legal fees, investor relations and audit fees.

Settlement Costs

	Years Ended December 31,			2018 / 2017 Comparison		2017 / 2016 Comparison	
	2018	2017	2016	$	%	$	%
	($ in thousands)						
Settlement costs	$ (667)	$ 2,073	$ —	$(2,740)	(132)%	$2,073	100%

In December 2017, we entered into a MOU related to our class action settlement that included the issuance of the 2.0 million Settlement Warrants to purchase shares of our common stock. The Settlement Warrants were revalued at each balance sheet date prior to issuance. On July 16, 2018, we issued and delivered the Settlement Warrants.

In 2018, settlement costs decreased attributable to the decreases in the fair value of the Settlement Warrants that principally resulted from a lower volatility rate of our common stock used in the Black-Scholes valuations relative to prior periods.

Change in Fair Value of PIPE Warrant Liability

	Years Ended December 31,			2018 / 2017 Comparison		2017 / 2016 Comparison	
	2018	2017	2016	$	%	$	%
	($ in thousands)						
Change in fair value of PIPE Warrant liability	$ 19,919	$ (33,740)	$ 4,751	$53,659	(159)%	$(38,491)	(810)%

In May 2016, we issued the PIPE Warrants in connection with a private placement financing and recorded the warrants as a liability. The PIPE Warrants are subject to revaluation at each balance sheet date.

In 2018, we recorded an approximate non-cash gain of $19.9 million in our Statement of Operations attributable to the decrease in the fair value of the PIPE Warrant liability that principally resulted from a lower stock price of $1.60 on December 31, 2018 compared to the stock price of $2.79 on December 31, 2017.

In 2017, we recorded an approximate non-cash loss of $33.7 million in our Statement of Operations attributable to the increase in the fair value of the PIPE Warrant liability that principally resulted from a higher stock price of $2.79 on December 31, 2017 compared to the stock price of $0.54 on December 31, 2016.

In 2016, we recorded an approximate $4.8 million non-cash gain in our Statement of Operations attributable to the decrease in the fair value of the warrant liability that principally resulted from a lower stock price of $0.54 on December 31, 2016 as compared to the stock price of $0.89 on the date of issuance of the PIPE warrants in May 2016.

Other Income (Expense)

	Years Ended December 31,			2018 / 2017 Comparison		2017 / 2016 Comparison	
	2018	2017	2016	$	%	$	%
	($ in thousands)						
Other income (expense)	$ 2,300	$ —	$ (195)	$2,300	100%	$ 195	(100)%

In December 2018, we entered into the AV-380 Transfer Agreement with Novartis, pursuant to which Novartis was obligated to make a one-time payment to us of $2.3 million. The $2.3 million payment due from Novartis was not considered a revenue transaction due to the effective termination of the Novartis Agreement on August 28, 2018 and was instead considered other income.

Interest Expense, net

	Years Ended December 31,			2018 / 2017 Comparison		2017 / 2016 Comparison	
	2018	2017	2016	$	%	$	%
	($ in thousands)						
Interest expense, net	$ (2,191)	$ (2,373)	$ (1,949)	$ 182	(8)%	$ (424)	22%

In December 2017, we refinanced our debt facility, the terms of which included a reduction in the then interest rate from 11.9% to 9.45%, an extension in the interest-only period by no less than 12 months, which could be extended up to a maximum of 24 months, assuming the achievement of specified milestones relating to the development of tivozanib, and an extension in the loan maturity from December 2019 to July 2021.

In 2018, the interest rate increased to 9.70%, 9.95% and 10.20% in June 2018, September 2018 and December 2018, respectively, due to corresponding increases in the prime interest rate, which is a component of the overall interest rate.

We anticipate that interest expense in 2019 will remain at current levels. In November 2018, Hercules granted the first 6-month extension of the interest-only period, which resulted in the deferment of principal payments until August 1, 2019.

Provision for Income Taxes

	Years Ended December 31,			2018 / 2017 Comparison		2017 / 2016 Comparison	
	2018	2017	2016	$	%	$	%
	($ in thousands)						
Provision for Income Taxes	$ —	$ 101	$ 101	$ (101)	(100)%	$ —	—%

We recorded a $0.1 million tax provision for foreign withholding taxes in each of the years ended December 31, 2017 and 2016 in connection with partnership payments from CANbridge. In March 2016, we received the $1.0 million upfront payment upon the execution of the collaboration and license agreement. In 2017, we received a total of $1.0 million in reimbursement payments related to manufacturing development activities conducted by us prior to the Effective Date of the collaboration and license agreement.

Contractual Obligations and Commitments

The following table summarizes our non-cancellable contractual obligations at December 31, 2018 (in thousands):

	Total	Less than 1 Year	1 to 3 Years	3 to 5 Years	More than 5 Years
Hercules loan agreement (1)	$ 24,527	$ 6,122	$ 18,405	$ —	$ —
Clinical trial costs and contract research (2)	13,668	12,456	1,212	—	—
Operating leases (3)	60	60	—	—	—
SVH time-based milestone (4)	2,300	2,300	—	—	—
Total contractual obligations	$ 40,555	$ 20,938	$ 19,617	$ —	$ —

(1) Includes scheduled interest payments and end of term payments totaling $1.1 million due in connection with the 2016 Amendment and 2017 Loan Agreement.

(2) Clinical trial costs and contract research principally include contracts for human clinical trials and clinical drug manufacturing and distribution. In the event a contract is terminated prior to the planned completion, the amount paid under such contracts may be less than the amounts presented.

(3) We sublease our principal office facility at One Broadway in Cambridge, MA. Our lease arrangement is cancellable within 30 days' notice to our landlord. As a result, our operating lease obligation as of December 31, 2018 is the January 2019 rent payable to our landlord.

(4) Under our license agreement with Kyowa Hakko Kirin, we are required to make certain milestone payments upon the achievement of specified regulatory milestones. We are also required to pay 30% of certain amounts we receive from sublicensees, including upfront license fees, milestone payments and royalties, other than amounts we receive in respect of research and development funding or equity investments, subject to certain limitations. Also, under our license agreement with St. Vincent's, we are required to make certain milestone payments 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. In addition, we are also obligated to pay Biogen a percentage of milestone payments received by AVEO from future partnerships after March 28, 2016 and single digit royalty payments on net sales related to the sale of ErbB3 products, if any, up to a cumulative maximum amount of $50.0 million. At this time, we cannot reasonably estimate when or if we may be required to make other additional payments to Kyowa Hakko Kirin, St. Vincent's or Biogen and have not included any additional amounts in the table above. For example, 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. In addition, we are required to make future milestone payments to St. Vincent's Hospital, up to an aggregate total of $14.4 million (exclusive of the $2.3 million milestone payment due in January 2019 as 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 under the license agreement, depending on the sublicensed territory. 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.

(5) As discussed in Note 4 to our consolidated financial statements included elsewhere in this Annual Report on Form 10K, we have executed license agreements for patented technology and other technology related to research projects, including technology to humanize ficlatuzumab and other antibody product candidates. The license agreements required us to pay non-refundable license fees upon execution, and in certain cases, require milestone payments upon the achievement of defined development goals. We have not included any additional milestone payments in the table above as we are not able to make a reasonable estimate of the probability and timing of such payments, if any. In addition to the amounts in the table above, three of the four agreements include sales and development milestones of up to $22.5 million. $5.5 million and $4.2 million per product, respectively, and single digit royalties as a percentage, and one agreement includes a $1.0 million license payment per product.

Liquidity and Capital Resources

We have financed our operations to date primarily through the sale of private placements and public offerings of our common stock and preferred stock, license fees, milestone payments and research and development funding from strategic partners, and loan proceeds. As of December 31, 2018, we had cash, cash equivalents and marketable securities of approximately $24.4 million. See "—Liquidity and Going Concern" below and Note 1 to the consolidated financial statements included elsewhere in this Annual Report on Form 10-K for a further discussion of our liquidity and the conditions and events which raise substantial doubt regarding our ability to continue as a going concern. Currently, our funds are invested in a U.S. government money market fund and corporate debt securities, including commercial paper. The following table sets forth the primary sources and uses of cash for each of the periods set forth below (in thousands):

	Years Ended December 31,		
	2018	2017	2016
		(in thousands)	
Net cash used in operating activities	$ (25,026)	$ (19,164)	$ (31,066)
Net cash provided by (used in) investing activities	18,579	(10,402)	(764)
Net cash provided by financing activities	15,925	29,419	20,292
Net increase (decrease) in cash and cash equivalents	$ 9,478	$ (147)	$ (11,538)

Our operating activities used cash of $25.0 million, $19.2 million and $31.1 in 2018, 2017 and 2016, respectively. Cash used in operations was principally due to our net loss adjusted for non-cash items and changes in working capital.

Our investing activities provided cash of $18.6 million in 2018, and used cash of $10.4 million and $0.8 million in 2017 and 2016, respectively, principally due to net changes in the maturities and purchases of marketable securities.

Our financing activities provided cash of $15.9 million, $29.4 million and $20.3 million in 2018, 2017 and 2016, respectively. In 2018, we raised approximately $15.9 million net from the issuance of our common stock, including approximately $5.1 million in net proceeds from an underwritten public offering of 2.5 million shares of our common stock in August 2018, $10.3 million in net proceeds from the sale of approximately 4.7 million shares of our common stock pursuant to the Leerink Sales Agreement in the fourth quarter of 2018 and approximately $1.0 million from the exercise of PIPE Warrants and stock options, offset by a $0.5 million end-of-term debt payment in January 2018 in connection with the 2014 Amendment of our loan First Loan Agreement with Hercules (all capitalized terms being defined in the section below, "Credit Facilities"). In 2017, we raised approximately $29.5 million in net cash proceeds, including $15.4 million from an underwritten public offering of 34.5 million shares of our common stock, $8.8 million from sales of 6.5 million shares of our common stock under our former Sales Agreement with FBR & Co., or FBR, (formerly MLV & Co. LLC), $5.0 million from additional borrowings under our Hercules Loan Agreement and $0.3 million from the issuance of 0.3 million shares of our common stock upon the exercise of 0.3 million PIPE warrants, offset by $0.1 million in debt issuance costs related to the 2017 Loan Agreement with Hercules. In 2016, we raised approximately $20.3 million in net cash proceeds, including $15.4 million in net proceeds from a private placement of 17,642,842 units, each including one share of our common stock and a warrant to purchase one share of our common stock, and $4.9 million in net proceeds from additional borrowings under our Hercules Loan Agreement.

Settlement Warrants

On July 16, 2018, we issued and delivered 2.0 million Settlement Warrants to purchase shares of our common stock for a one-year period after the date of issuance at an exercise price equal to $3.00 per share. Refer to the section above, "*Class Action Settlement and Settlement Warrants*" for further discussion.

Sales Agreement with SVB Leerink

On November 30, 2017, we filed a shelf registration statement on Form S-3 with the SEC, which we refer to as the 2017 Shelf. The 2017 Shelf (File No. 333-221873) was declared effective by the SEC on December 15, 2017 and covers the offering, issuance and sale from time to time of up to $200 million of our common stock, preferred stock, debt securities, warrants and/or units. The 2017 Shelf was filed to replace our then-existing 2015 shelf registration statement, which was terminated upon the 2017 Shelf being declared effective by the SEC on December 15, 2017.

In February 2018, we entered into the Leerink Sales Agreement pursuant to which we may issue and sell shares of our common stock from time to time up to an aggregate amount of $50 million, at our option, through SVB Leerink as our sales agent, with any sales of common stock through SVB Leerink being made by any method that is deemed an "at-the-market" offering as defined in Rule 415 promulgated under the Securities Act of 1933, as amended, or in other transactions. Any such shares of common stock will be sold pursuant to a prospectus supplement filed under the 2017 Shelf. We agreed to pay SVB Leerink a commission of up to 3% of the gross proceeds of any sales of common stock pursuant to the Leerink Sales Agreement. In the fourth quarter of 2018, we sold approximately 4.7 million shares pursuant to the Leerink Sales Agreement, resulting in approximately $10.3 million in proceeds, net of commissions.

In February 2019, we sold approximately 12.5 million shares pursuant to the SVB Leerink Sales Agreement, resulting in proceeds of approximately $7.5 million, net of commissions.

Public Offering – August 2018

On August 21, 2018, we closed an underwritten public offering of 2.5 million shares of our common stock at the public offering price of $2.26 per share for gross proceeds of approximately $5.7 million. Two greater than 5% stockholders, including an entity affiliated with New Enterprise Associates and another stockholder purchased approximately 2.0 million shares in this offering at the same public offering price per share as the other investors. The net offering proceeds to us were approximately $5.1 million after deducting underwriting discounts and estimated offering expenses payable by us.

Public Offering – March 2017

On March 31, 2017, we closed an underwritten public offering of 34.5 million shares of our common stock, including the exercise in full by the underwriter of its option to purchase 4.5 million shares, at the public offering price of $0.50 per share for gross proceeds of approximately $17.3 million. Certain of our executive officers and a director purchased an aggregate of 420,000 shares and an entity affiliated with New Enterprise Associates purchased 6.0 million shares in this offering at the same public offering price per share as the other investors. The net offering proceeds to us were approximately $15.4 million after deducting underwriting discounts and estimated offering expenses payable by us.

Private Placement / PIPE Warrants

In May 2016, we entered into a securities purchase agreement with a select group of qualified institutional buyers, institutional accredited investors and accredited investors pursuant to which we sold 17,642,482 units, at a price of $0.965 per unit, for gross proceeds of approximately $17.0 million. Each unit consisted of one share of our common stock and a PIPE Warrant to purchase one share of our common stock. The PIPE Warrants have an exercise price of $1.00 per share and are exercisable in any manner at any time for a period of five years from the date of issuance. Certain of our directors and executive officers purchased an aggregate of 544,039 units in this offering at the same price as the other investors. The net offering proceeds to us were approximately $15.4 million after deducting placement agent fees and other offering expenses payable by us. As of December 31, 2018, PIPE Warrants exercisable for 803,108 shares of common stock had been exercised, for approximately $0.8 million in cash proceeds, and PIPE Warrants exercisable for 16,839,375 shares of common stock were outstanding. In July 2017, we issued to Hercules Capital Inc. 259,067 shares of common stock upon its exercise of all of its PIPE Warrants, and we received approximately $0.3 million in cash proceeds. In 2018, PIPE Warrants with respect to 544,041 shares of common stock underlying such PIPE Warrants were exercised, and we issued 544,041 shares of our common stock and received approximately $0.5 million in cash proceeds.

Sales Agreement with FBR

In February 2015, we entered into a sales agreement, which we refer to as the FBR Sales Agreement, with FBR & Co. and MLV & Co. LLC, or together FBR, pursuant to which we issued and sold shares of our common stock from time to time up to an aggregate amount of $17.9 million, at our option, through FBR as our sales agent, with any sales of common stock through FBR being made by any method that is deemed an "at-the-market" offering as defined in Rule 415 promulgated under the Securities Act or in other transactions, in each case pursuant to an effective shelf registration statement on Form S-3. We agreed to pay FBR a commission of up to 3% of the gross proceeds of any sales of common stock pursuant to the FBR Sales Agreement.

In June 2017, we sold approximately 6.5 million shares pursuant to the FBR Sales Agreement, as amended, resulting in proceeds of approximately $8.8 million, net of commissions and issuance costs. The FBR Sales Agreement has expired.

Credit Facilities

On May 28, 2010, we entered into a loan and security agreement with Hercules Capital Inc. and certain of its affiliates, or the First Loan Agreement. The First Loan Agreement was subsequently amended in March 2012, or the 2012 Amendment; September 2014, or the 2014 Amendment and May 2016, or the 2016 Amendment. In December 2017, we refinanced the First Loan Agreement, as amended, by entering into an amended and restated loan and security agreement, or the 2017 Loan Agreement, with Hercules Funding III, LLC and Hercules Capital, Inc., which we collectively refer to as Hercules.

Pursuant to the 2014 Amendment, we received $10.0 million in additional loan proceeds from Hercules and were required to make an end-of-term payment of approximately $0.5 million on January 1, 2018. This payment was made on the first business day of 2018.

Pursuant to the 2016 Amendment, we received additional loan proceeds from Hercules, in an aggregate amount of $10.0 million, received in installments of $5.0 million in each of May 2016 and June 2017, which increased the aggregate outstanding principal balance under the First Loan Agreement to $20.0 million. We are required to make an end-of-term payment totaling $0.3 million on December 1, 2019. The 2016 Amendment included a financial covenant that required us to maintain an unrestricted cash position greater than or equal to $10.0 million through the date of completion of our TIVO-3 trial with results that were satisfactory to Hercules. Principal payments were scheduled to commence on January 1, 2018 and the loan was scheduled to mature on December 1, 2019.

In December 2017, we entered into the 2017 Loan Agreement to refinance our existing loan facility with Hercules and to retire the $20.0 million in secured debt then-outstanding under the First Loan Agreement. Per the terms of the 2017 Loan Agreement, the new $20.0 million loan facility has a 42-month maturity from closing, no financial covenants, a lower interest rate and an interest-only period of no less than 12 months, which could be extended up to a maximum of 24 months, assuming the achievement of specified milestones relating to the development of tivozanib. Per the 2017 Loan Agreement, Hercules did not receive any additional warrants to purchase shares of our common stock and no longer has the option, subject to our written consent, to participate in our future equity financings up to $2.0 million through the purchase of our common stock either with cash or through the conversion of outstanding principal under the loan.

Pursuant to the 2017 Loan Agreement, the loan maturity date has been revised from December 2019 to July 2021. We were not required to make principal payments until February 1, 2019, at which time we would have been required to make 29 equal monthly payments of principal and interest, in the approximate amount of $0.8 million through July 2021. An additional end-of-term payment of approximately $0.8 million is due on July 1, 2021, which increased the total end-of-term payments under the 2014 Amendment, 2016 Amendment and 2017 Loan Agreement to approximately $1.6 million. The end-of-term payments under the 2014 Amendment, in the approximate amount of $0.5 million, and the 2016 Amendment, in the amount of $0.3 million, continued to be due on their original due dates of January 1, 2018 and December 1, 2019, respectively. The financial covenant per the 2016 Amendment to maintain an unrestricted cash position greater than or equal to $10.0 million through the date of completion of our TIVO-3 trial with results that are satisfactory to Hercules has been removed. Per the 2017 Loan Agreement, the interest rate decreased from 11.9% to 9.45%.

We must make interest payments on the principal balance of the loan each month it remains outstanding. Per annum interest is payable on the loan balance at the greater of 9.45% and an amount equal to 9.45% plus the prime rate minus 4.75%, as determined daily, provided however, that the per annum interest rate shall not exceed 15.0%. In 2018, the interest rate increased to 9.70%, 9.95% and 10.20% in June 2018, September 2018 and December 2018, respectively, due to corresponding increases in the prime rate.

The interest-only period could be extended by two 6-month deferrals of principal payments upon the achievement of specified milestones relating to the development of tivozanib, subject to confirmation by Hercules at its reasonable discretion.

In November 2018, Hercules granted the first 6-month extension of the interest-only period. Accordingly, this resulted in the deferment of principal payments until August 1, 2019, at which time we will be required to make 24 equal monthly payments of principal and interest, in the approximate amount of $0.9 million through July 2021. The loan maturity date of July 1, 2021 remains unchanged. The end-of-term payments under the 2016 Amendment, in the amount of $0.3 million, and the 2017 Loan Agreement, in the approximate amount of $0.8 million, continue to be due on their original due dates of December 1, 2019 and July 1, 2021, respectively.

We have determined that the risk of subjective acceleration under the material adverse events clause included in the 2017 Loan Agreement is remote and, therefore, have classified the outstanding principal amount in current and long-term liabilities based on the timing of scheduled principal payments. As of December 31, 2018, we are in compliance with all of the loan covenants and, through the date of this filing, the lenders have not asserted any events of default under the loan. We do not believe that there has been a material adverse change as defined in the 2017 Loan Agreement. The loans are secured by a lien on all of our personal property (other than intellectual property), whether owned as of, or acquired after, the date of the First Loan Agreement.

Liquidity and Going Concern

We have devoted substantially all of our resources to our drug development efforts, comprised of research and development, manufacturing, conducting clinical trials for our product candidates, protecting our intellectual property and general and administrative functions relating to these operations. Our future success is dependent on our ability to develop our product candidates and ultimately upon our ability to attain profitable operations. We anticipate that we will continue to incur significant operating losses for the next several years as we incur expenses to continue to execute on our clinical development strategy to advance our preclinical and clinical stage assets. We will require substantial additional funds to continue our development programs and to fulfill our planned operating goals. In particular, our currently planned operating and capital requirements include the need for substantial working capital to support our development activities for tivozanib. For example, we estimate that the 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, 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 specified percentage of sublicense revenue in certain instances.

During the year ended December 31, 2018, we received approximately $23.6 million in funding, including approximately $7.1 million in partnership funding and approximately $16.4 million related to the sale of our common stock. The approximate $7.1 million in partnership funding included $4.0 million in milestone payments by EUSA for reimbursement approvals of RCC in the United Kingdom and Germany, $2.0 million in a milestone payment by CANbridge for the regulatory approval of an IND application for a clinical study of AV-203 in ESCC, approximately $0.3 million in royalties from the sales of FOTIVDA by EUSA and approximately $0.8 million in cost sharing payments. The approximate $16.4 million in funding from the sale of our common stock included the approximate $5.1 million in net proceeds from the sale of 2.5 million shares of our common stock in a public offering in August 2018, the approximate $10.3 million in net proceeds from the sale of approximately 4.7 million shares of our common stock pursuant to our Leerink Sales Agreement in the fourth quarter of 2018, and approximately $1.0 million related to the exercise of PIPE Warrants and stock options.

As of December 31, 2018, we had approximately $24.4 million in cash, cash equivalents and marketable securities, working capital of $9.8 million and an accumulated deficit of $595.0 million. 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 that 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.

Our plans to address this condition include pursuing one or more of the following options to secure additional funding, none of which can be guaranteed or are entirely within our control:

- Earn royalty payments pursuant to the EUSA Agreement. In August 2017, EUSA obtained marketing approval from the EMA for tivozanib (FOTIVDA) for the treatment of RCC.
- Earn milestone payments pursuant to our collaboration and license agreements or restructure / monetize existing potential milestone and/or royalty payments under those collaboration and license agreements.
- Raise funding through the possible additional sales of our common stock, including public or private equity financings.
- Partner a portion or all rights to the Company's portfolio candidates to secure potential additional non-dilutive funds.

Pursuant to our EUSA Agreement, we are entitled to receive up to an additional $6.0 million in milestone payments of $2.0 million per country upon reimbursement approval for RCC, if any, in each of France, Italy and Spain, and an additional $2.0 million milestone payment for the grant of marketing approval, if any, in three of the licensed countries outside of the EU, as mutually agreed by the parties. These milestone payments are subject to the 30% sublicense fee payable to KHK. We are also eligible to receive an additional research and development reimbursement payment from EUSA of 50% of the total costs for our TIVO-3 trial, up to $20.0 million, if EUSA elects to opt-in to that study. This research and development reimbursement payment would not be subject to the 30% sublicense fee payable to KHK, subject to certain limitations.

There can be no assurance, however, that we will receive cash proceeds from any of these potential resources or to the extent cash proceeds are received such proceeds would be sufficient to support our current operating plan for at least the next twelve months from the date of filing this Annual Report on Form 10-K.

Pursuant to the requirements of Accounting Standards Codification (ASC) 205-40, *Disclosure of Uncertainties about an Entity's Ability to Continue as a Going Concern*, management must evaluate whether there are conditions or events, considered in the aggregate, that raise substantial doubt about our ability to continue as a going concern within one year after the date that the financial statements are issued. This evaluation initially does not take into consideration the potential mitigating effect of management's plans that have not been fully implemented as of the date the financial statements are issued. When substantial doubt exists under this methodology, management evaluates whether the mitigating effect of its plans sufficiently alleviates substantial doubt about our ability to continue as a going concern. The mitigating effect of management's plans, however, is only considered if both (1) it is probable that the plans will be effectively implemented within one year after the date that the financial statements are issued, and (2) it is probable that the plans, when implemented, will mitigate the relevant conditions or events that raise substantial doubt about the entity's ability to continue as a going concern within one year after the date that the financial statements are issued.

Under ASC 205-40, the future receipt of potential funding from our collaborators and other resources cannot be considered probable at this time because none of our current plans have been finalized at the time of filing this Annual Report on Form 10-K and the implementation of any such plan is not probable of being effectively implemented as none of the plans are entirely within our control. Accordingly, substantial doubt is deemed to exist about our ability to continue as a going concern within one year after the date these financial statements are issued.

We believe that our approximate $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 a 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 our Leerink Sales Agreement and no additional sales of equity through the exercise of our outstanding PIPE Warrants or the Settlement 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.

There are numerous risks and uncertainties associated with research, development and commercialization of pharmaceutical products. Accordingly, our future funding requirements may vary from our current expectations and will 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 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 above 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 then 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.

Off-Balance Sheet Arrangements

We did not have, during the periods presented, and we do not currently have, any off-balance sheet arrangements, as defined under applicable SEC rules.

ITEM 7A. Quantitative and Qualitative Disclosures About Market Risk.

We are exposed to market risk related to changes in interest rates. As of December 31, 2018, we had cash, cash equivalents and marketable securities of approximately $24.4 million. Currently, our funds are invested in a U.S. government money market fund and corporate debt securities, including commercial paper. We do not hold any of these instruments for trading or speculative purposes. Our funds are invested in accordance with investment guidelines as approved by our Board of Directors.

Our primary exposure to market risk is interest rate sensitivity, which is affected by changes in the general level of U.S. interest rates, particularly because our investments are in short-term cash equivalents. Our cash equivalents and marketable securities are subject to interest rate risk and could fall in value if market interest rates increase. Due to the short-term duration of our investment portfolio and the low risk profile of our investments, an immediate 10% change in interest rates would not have a material effect on the fair market value of our portfolio. We have the ability to hold our cash equivalents until maturity, and therefore we would not expect our operating results or cash flows to be affected to any significant degree by the effect of a change in market interest rates on our investments. We do not currently have any auction rate securities.

Our loans payable are subject to interest rate risk. As of December 31, 2018, our aggregate principal balance outstanding on our 2017 Loan Agreement with Hercules was $20.0 million. Per annum interest is payable on the principal balance of the loan each month it remains outstanding at the greater of 9.45% or an amount equal to 9.45% plus the prime rate minus 4.75% as determined daily, provided however, that the per annum interest rate shall not exceed 15.0%. As of December 31, 2018, the interest rate was 10.20%. For every 1% increase in the prime rate over 4.75%, given the amount of debt outstanding under the 2017 Loan Agreement as of December 31, 2018, we would have an increase in future annual cash outflows of approximately $0.2 million over the next twelve-month period as a result of such 1% increase.

We are also exposed to market risk related to change in foreign currency exchange rates. We contract with contract research organizations and investigational sites that are located around the world. We are subject to fluctuations in foreign currency rates in connection with these agreements. We do not currently hedge our foreign currency exchange rate risk.

ITEM 8. Financial Statements and Supplementary Data

AVEO PHARMACEUTICALS, INC.

INDEX TO CONSOLIDATED FINANCIAL STATEMENTS

REPORT OF INDEPENDENT REGISTERED PUBLIC ACCOUNTING FIRM

To the Stockholders and the Board of Directors of AVEO Pharmaceuticals, Inc.

Opinion on the Financial Statements

We have audited the accompanying consolidated balance sheets of AVEO Pharmaceuticals, Inc. (the "Company") as of December 31, 2018 and 2017, the related consolidated statements of operations, comprehensive loss, stockholders' deficit, and cash flows for each of the three years in the period ended December 31, 2018, and the related notes (collectively referred to as the "consolidated financial statements"). In our opinion, the consolidated financial statements present fairly, in all material respects, the financial position of the Company at December 31, 2018 and 2017, and the results of its operations and its cash flows for each of the three years in the period ended December 31, 2018, in conformity with U.S. generally accepted accounting principles.

We have also audited, in accordance with the standards of the Public Company Accounting Oversight Board (United States) (PCAOB), the Company's internal control over financial reporting as of December 31, 2018, based on criteria established in Internal Control – Integrated Framework issued by the Committee of Sponsoring Organizations of the Treadway Commission (2013 framework) and our report dated March 14, 2019 expressed an unqualified opinion thereon.

The Company's Ability to Continue as a Going Concern

The accompanying consolidated financial statements have been prepared assuming that the Company will continue as a going concern. As discussed in Note 1 to the financial statements, the Company will require additional capital to fund its current operating plan, and has stated that substantial doubt exists about the Company's ability to continue as a going concern. Management's evaluation of the events and conditions and management's plans regarding these matters are also described in Note 1. The consolidated financial statements do not include any adjustments that might result from the outcome of this uncertainty.

Adoption of New Accounting Standard

As discussed in Note 3 to the consolidated financial statements, the Company changed its method of accounting for revenue in 2018 due to the adoption of Accounting Standards Update (ASU) No. 2014-09, Revenue from Contracts with Customers (Topic 606), and the related amendments.

Basis for Opinion

These financial statements are the responsibility of the Company's management. Our responsibility is to express an opinion on the Company's financial statements based on our audits. We are a public accounting firm registered with the PCAOB and are required to be independent with respect to the Company in accordance with the U.S. federal securities laws and the applicable rules and regulations of the Securities and Exchange Commission and the PCAOB.

We conducted our audits in accordance with the standards of the PCAOB. Those standards require that we plan and perform the audit to obtain reasonable assurance about whether the financial statements are free of material misstatement, whether due to error or fraud. Our audits included performing procedures to assess the risks of material misstatement of the financial statements, whether due to error or fraud, and performing procedures that respond to those risks. Such procedures include examining, on a test basis, evidence regarding the amounts and disclosures in the financial statements. Our audits also included evaluating the accounting principles used and significant estimates made by management, as well as evaluating the overall presentation of the financial statements. We believe that our audits provide a reasonable basis for our opinion.

/s/ Ernst & Young LLP

We have served as the Company's auditor since 2003.
Boston, Massachusetts
March 14, 2019

AVEO PHARMACEUTICALS, INC.

Consolidated Balance Sheets
(In thousands, except par value amounts)

	December 31, 2018	December 31, 2017
Assets		
Current assets:		
Cash and cash equivalents	$ 24,427	$ 14,949
Marketable securities	—	18,576
Accounts receivable	3,026	402
Insurance recovery (Note 13)	—	15,000
Clinical trial retainers	126	1,027
Other prepaid expenses and other current assets	356	229
Total current assets	27,935	50,183
Other assets	—	15
Total assets	$ 27,935	$ 50,198
Liabilities and stockholders' deficit		
Current liabilities:		
Accounts payable	$ 3,499	$ 2,436
Accrued clinical trial costs and contract research	6,254	8,321
Other accrued liabilities	2,698	2,458
Loans payable, net of discount	3,254	—
Deferred revenue	1,658	395
Deferred research and development reimbursements	454	901
Estimated settlement liability (Note 13)	—	17,073
Other liabilities (Note 6)	300	540
Total current liabilities	18,117	32,124
Loans payable, net of current portion and discount	15,779	18,477
Deferred revenue	3,802	1,302
Deferred research and development reimbursements	—	222
PIPE Warrant liability (Note 7)	16,674	37,746
Other liabilities (Note 6)	790	1,090
Total liabilities	55,162	90,961
Stockholders' deficit:		
Preferred stock, $.001 par value: 5,000 shares authorized at each of December 31, 2018 and 2017; no shares issued and outstanding at each of December 31, 2018 and 2017	—	—
Common stock, $.001 par value: 250,000 shares authorized at each of December 31, 2018 and December 31, 2017; 126,485 and 118,325 shares issued and outstanding as of December 31, 2018 and 2017, respectively	126	118
Additional paid-in capital	567,655	546,092
Accumulated other comprehensive income (loss)	1	(4)
Accumulated deficit	(595,009)	(586,969)
Total stockholders' deficit	(27,227)	(40,763)
Total liabilities and stockholders' deficit	$ 27,935	$ 50,198

See accompanying notes.

AVEO PHARMACEUTICALS, INC.

Consolidated Statements of Operations
(In thousands, except per share amounts)

	Year Ended December 31,		
	2018	**2017**	**2016**
Revenues:			
Collaboration and licensing revenue	$ 4,947	$ 7,560	$ 2,515
Partnership royalties	462	19	—
	5,409	7,579	2,515
Operating expenses:			
Research and development	20,652	25,179	23,703
General and administrative	10,781	9,138	8,205
Settlement costs (Note 13)	(667)	2,073	—
	30,766	36,390	31,908
Loss from operations	(25,357)	(28,811)	(29,393)
Other income (expense), net:			
Interest expense, net	(2,191)	(2,373)	(1,949)
Change in fair value of PIPE Warrant liability	19,919	(33,740)	4,751
Other income (expense)	2,300	—	(195)
Other income (expense), net	20,028	(36,113)	2,607
Net loss before provision for income taxes	(5,329)	(64,924)	(26,786)
Provision for income taxes	—	(101)	(101)
Net loss	$ (5,329)	$ (65,025)	$ (26,887)
Basic net loss per share:			
Net loss per share	$ (0.04)	$ (0.61)	$ (0.39)
Weighted average number of common shares outstanding	120,592	105,930	69,268
Diluted net loss per share:			
Net loss per share	$ (0.19)	$ (0.61)	$ (0.39)
Weighted average number of common shares and dilutive common share equivalents outstanding	130,731	105,930	69,268

See accompanying notes.

AVEO PHARMACEUTICALS, INC.

Consolidated Statements of Comprehensive Loss
(In thousands)

	Year Ended December 31,		
	2018	2017	2016
Net loss	$ (5,329)	$ (65,025)	$ (26,887)
Other comprehensive income (loss):			
Unrealized gain (loss) on available-for-sale securities	5	(10)	9
Comprehensive loss	$ (5,324)	$ (65,035)	$ (26,878)

See accompanying notes.

AVEO PHARMACEUTICALS, INC.

Consolidated Statements of Stockholders' Deficit
(In thousands)

	Common Shares		Additional Paid-in Capital	Accumulated Other Comprehensive Income (Loss)	Accumulated Deficit	Total Stockholders' (Deficit) Equity
	Shares	Par Value				
Balance at December 31, 2015	58,182	$ 58	$ 512,201	$ (3)	$ (495,029)	$ 17,227
Issuance of common stock and warrants in a private placement, excluding to related parties (net of issuance costs of $1.6 million)	17,098	17	14,829	—	—	14,846
Issuance of common stock and warrants to related parties	544	1	524	—	—	525
Stock-based compensation expense related to equity-classified awards	—	—	999	—	—	999
Issuance of warrants in connection with a private placement	—	—	(9,344)	—	—	(9,344)
Issuance of warrants in connection with loans payable	—	—	667	—	—	667
Exercise of stock options	39	—	33	—	—	33
Issuance of common stock under employee stock purchase plan	—	—	2	—	—	2
Change in unrealized gain (loss) on investments	—	—	—	9	—	9
Net loss	—	—	—	—	(26,887)	(26,887)
Balance at December 31, 2016	75,863	$ 76	$ 519,911	$ 6	$ (521,916)	$ (1,923)
Adjustment related to adoption of new stock option forfeiture standard	—	—	28	—	(28)	—
Issuance of common stock in a public offering, excluding to related parties (net of issuance costs of $1.8 million)	28,080	28	12,191	—	—	12,219
Issuance of common stock to related parties	6,420	6	3,204	—	—	3,210
Issuance of common stock from the FBR sales agreement (net of issuance costs of $0.2 million)	6,470	6	8,810	—	—	8,816
Stock-based compensation expense related to equity-classified awards	—	—	1,089	—	—	1,089
Issuance of common stock in connection with warrant exercises	1,475	2	257	—	—	259
Reduction in PIPE Warrant liability in connection with warrant exercises	—	—	587	—	—	587
Exercise of stock options	17	—	15	—	—	15
Change in unrealized gain (loss) on investments	—	—	—	(10)	—	(10)
Net loss	—	—	—	—	(65,025)	(65,025)
Balance at December 31, 2017	118,325	$ 118	$ 546,092	$ (4)	$ (586,969)	$ (40,763)
Adjustment related to adoption of new revenue recognition standard ASC 606	—	—	—	—	(2,711)	(2,711)
Issuance of common stock in a public offering, excluding to related parties (net of issuance costs of $0.6 million)	509	—	597	—	—	597
Issuance of common stock to related parties	1,991	2	4,498	—	—	4,500
Issuance of common stock from the SVB Leerink sales agreement (net of issuance costs of $0.2 million)	4,708	5	10,325	—	—	10,330
Issuance of Settlement Warrants in connection with a class action settlement (Note 13)	—	—	1,406	—	—	1,406
Stock-based compensation expense related to equity-classified awards	—	—	2,546	—	—	2,546
Issuance of common stock in connection with warrant exercises	544	1	543	—	—	544
Reduction in PIPE Warrant liability in connection with warrant exercises	—	—	1,153	—	—	1,153
Exercise of stock options	399	—	478	—	—	478
Issuance of common stock under employee stock purchase plan	9	—	17	—	—	17
Change in unrealized gain (loss) on investments	—	—	—	5	—	5
Net loss	—	—	—	—	(5,329)	(5,329)
Balance at December 31, 2018	**126,485**	**$ 126**	**$ 567,655**	**$ 1**	**$ (595,009)**	**$ (27,227)**

See accompanying notes.

AVEO PHARMACEUTICALS, INC.

Consolidated Statements of Cash Flows
(In thousands)

	Year Ended December 31,		
	2018	2017	2016
Operating activities			
Net loss	$ (5,329)	$ (65,025)	$ (26,887)
Adjustments to reconcile net loss to net cash used in operating activities:			
Depreciation and amortization	—	—	30
Stock-based compensation	2,546	1,089	999
Non-cash interest expense	556	514	465
Non-cash change in fair value of PIPE warrant liability	(19,919)	33,740	(4,751)
Non-cash charge for settlement costs (Note 13)	(667)	2,073	—
Amortization of premium and discount on investments	3	68	14
Changes in operating assets and liabilities:			
Accounts receivable	(2,624)	625	3,614
Insurance recovery (Note 13)	15,000	(15,000)	—
Prepaid expenses and other current assets	774	684	(340)
Other noncurrent assets	15	955	(827)
Accounts payable	1,063	250	760
Accrued clinical trial costs and contract research	(2,067)	4,323	2,032
Other accrued liabilities	240	927	(609)
Settlement liability (Note 13)	(15,000)	15,000	(4,000)
Deferred revenue	1,052	(510)	(1,488)
Deferred research and development reimbursements	(669)	1,123	—
Other liabilities	—	—	(78)
Net cash used in operating activities	(25,026)	(19,164)	(31,066)
Investing activities			
Purchases of marketable securities	(6,733)	(34,852)	(29,421)
Proceeds from maturities and sales of marketable securities	25,312	24,450	28,664
Purchases of property and equipment	—	—	(7)
Net cash provided by (used in) investing activities	18,579	(10,402)	(764)
Financing activities			
Proceeds from issuance of common stock and warrants, net of issuance costs	11,471	21,294	14,846
Proceeds from issuance of common stock and warrants to related parties	4,500	3,210	525
Proceeds from issuance of loan payable and warrants	—	5,000	5,000
Proceeds from issuance of stock for stock-based compensation arrangements	494	15	36
Payment of loan maturity fees (Note 6)	(540)	—	—
Payments of debt issuance costs	—	(100)	(115)
Net cash provided by financing activities	15,925	29,419	20,292
Net increase (decrease) in cash and cash equivalents	9,478	(147)	(11,538)
Cash and cash equivalents at beginning of period	14,949	15,096	26,634
Cash and cash equivalents at end of period	$ 24,427	$ 14,949	$ 15,096
Supplemental cash flow information			
Cash paid for interest	$ 1,986	$ 2,069	$ 1,539
Non-cash adjustment			
Increase to deferred revenue due to adoption of ASC 606 - transition adjustment on January 1, 2018	$ 2,711	$ —	$ —
Non-cash financing activity			
Fair value of warrants issued in connection with a class action settlement (Note 13)	$ 1,406	$ —	$ —
Fair value of warrants issued in connection with long term debt	$ —	$ —	$ 667
Fair value of warrants issued in connection with private placement	$ —	$ —	$ 9,344

See accompanying notes.

(1) Organization

AVEO Pharmaceuticals, Inc. (the "Company") is a biopharmaceutical company seeking to advance targeted medicines for oncology and other unmet medical needs. The Company is working to develop and commercialize its lead candidate tivozanib in North America as a treatment for advanced or metastatic renal cell carcinoma ("RCC"). In November 2018, the Company announced that its 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 (the "TIVO-3 trial") met its primary endpoint of progression-free survival ("PFS"). Data for the secondary endpoint of the TIVO-3 trial, overall survival ("OS"), was not mature as of the time of the final PFS analysis. In January 2019, the U.S. Food and Drug Administration (the "FDA") recommended that the Company not submit a new drug application ("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 Company's previously completed phase 3 trial for tivozanib in the first-line treatment of RCC (the "TIVO-1 trial"). Following discussion with the FDA, the Company has extended the timeline for the TIVO-3 trial OS analysis and plans to conduct another interim OS analysis in August 2019. The Company anticipates reporting the results of this analysis in the fourth quarter of 2019, and plans to provide an update regarding the potential submission of an NDA for tivozanib to the FDA.

The Company is leveraging several collaborations in the development of tivozanib. The Company has sublicensed tivozanib, marketed under the brand name FOTIVDA®, for oncological indications in Europe and other territories outside of North America. Through the Company's partner, tivozanib is approved in the European Union (the "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 ("VEGFR") and mTOR pathway inhibitor-naïve following disease progression after one prior treatment with cytokine therapy for RCC. The Company also has clinical collaborations to study tivozanib in combination with immune checkpoint inhibitors in RCC and in hepatocellular carcinoma ("HCC"). The Company is 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 (the "TiNivo trial"). Leveraging early monotherapy results in HCC, the Company has 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 the Company's strategy, the Company has also entered into partnerships to help fund the development and commercialization of its other product candidates. Ficlatuzumab, a hepatocyte growth factor ("HGF") inhibitory antibody, is currently being tested in several investigator sponsored studies jointly funded by the Company and one of its development partners for the potential treatment of squamous cell carcinoma of the head and neck, acute myeloid leukemia, and pancreatic cancer. The Company's partner for AV-203, an anti-ErbB3 monoclonal antibody, is planning to initiate clinical studies in China in 2019 in esophageal squamous cell carcinoma ("ESCC"), and has committed to funding the development of AV-203 through proof-of-concept. The Company recently regained the rights to AV-380, a humanized IgG1 inhibitory monoclonal antibody targeting growth differentiation factor 15 ("GDF15"), a divergent member of the TGF-ß family, for the potential treatment of cancer cachexia, and is working to initiate preclinical toxicology studies mid-2019 to support the potential filing of an investigational new drug application ("IND") with the FDA. The Company is evaluating options for the development of its preclinical AV-353 platform which targets the Notch 3 pathway.

As used throughout these consolidated financial statements, the terms "AVEO," and the "Company" refer to the business of AVEO Pharmaceuticals, Inc. and its two wholly-owned subsidiaries, AVEO Pharma Limited and AVEO Securities Corporation.

Liquidity and Going Concern

The Company has financed its operations to date primarily through private placements and public offerings of its common stock and preferred stock, license fees, milestone payments and research and development funding from strategic partners, and loan proceeds. The Company has devoted substantially all of its resources to its drug development efforts, comprising research and development, manufacturing, conducting clinical trials for its product candidates, protecting its intellectual property and general and administrative functions relating to these operations. The future success of the Company is dependent on its ability to develop its product candidates and ultimately upon its ability to attain profitable operations. As of December 31, 2018, the Company had cash, cash equivalents and marketable securities totaling approximately $24.4 million, working capital of $9.8 million and an accumulated deficit of $595.0 million.

The Company is subject to a number of risks, including the need for substantial additional capital for clinical research and product development. As of December 31, 2018, the Company had approximately $24.4 million in cash, cash equivalents and marketable securities. In February 2019, the Company sold approximately 12.5 million shares of its common stock pursuant to its sales agreement with SVB Leerink (the "Leerink Sales Agreement") and received approximately $7.5 million in net proceeds. Based on its available cash resources, the Company does 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 the Company's ability to continue as a going concern.

The Company's plans to address this condition include pursuing one or more of the following options to secure additional funding, none of which can be guaranteed or are entirely within the Company's control:

- Earn royalty payments pursuant to the Company's license agreement with EUSA Pharma (UK) Limited (the "EUSA Agreement"). In August 2017, EUSA Pharma (UK) Limited ("EUSA") obtained marketing approval from the European Medicines Agency (the "EMA") for tivozanib (FOTIVDA) for the treatment of RCC.
- Earn milestone payments pursuant to the collaboration and license agreements described in Note 4 or restructure / monetize existing potential milestone and/or royalty payments under those collaboration and license agreements.
- Raise funding through the possible additional sales of the Company's common stock, including public or private equity financings and / or sales of the Company's common stock under the Leerink Sales Agreement, as discussed in Note 7.
- Partner a portion or all rights to the Company's portfolio candidates to secure potential additional non-dilutive funds.

Pursuant to the EUSA Agreement, the Company is entitled to receive up to an additional $6.0 million in milestone payments of $2.0 million per country upon reimbursement approval for RCC, if any, in each of France, Italy and Spain, and an additional $2.0 million milestone payment for the grant of marketing approval, if any, in three of the licensed countries outside of the EU, as mutually agreed by the parties. These milestone payments are subject to the 30% sublicense fee payable to Kyowa Hakko Kirin Co., Ltd. (formerly Kirin Brewery Co., Ltd.) ("KHK") pursuant to the Company's license agreement with KHK (the "KHK Agreement"). The Company is also eligible to receive an additional research and development reimbursement payment from EUSA of 50% of the total costs for the Company's TIVO-3 trial, up to $20.0 million, if EUSA elects to opt-in to that study. This research and development reimbursement payment would not be subject to the 30% sublicense fee payable to KHK, subject to certain limitations. Refer to Note 4 "*Collaborations and License Agreements - KHK*" for further details.

There can be no assurance, however, that the Company will receive cash proceeds from any of these potential resources or to the extent cash proceeds are received such proceeds would be sufficient to support the Company's current operating plan for at least the next twelve months from the date of filing this Annual Report on Form 10-K.

Pursuant to the requirements of Accounting Standards Codification (ASC) 205-40, *Disclosure of Uncertainties about an Entity's Ability to Continue as a Going Concern* ("ASC 205-40") management must evaluate whether there are conditions or events, considered in the aggregate, that raise substantial doubt about the Company's ability to continue as a going concern within one year after the date that the financial statements are issued. This evaluation initially does not take into consideration the potential mitigating effect of management's plans that have not been fully implemented as of the date the financial statements are issued. When substantial doubt exists under this methodology, management evaluates whether the mitigating effect of its plans sufficiently alleviates substantial doubt about the Company's ability to continue as a going concern. The mitigating effect of management's plans, however, is only considered if both (1) it is probable that the plans will be effectively implemented within one year after the date that the financial statements are issued, and (2) it is probable that the plans, when implemented, will mitigate the relevant conditions or events that raise substantial doubt about the entity's ability to continue as a going concern within one year after the date that the financial statements are issued.

Under ASC 205-40, the future receipt of potential funding from the Company's collaborators and other resources cannot be considered probable at this time because none of the Company's current plans have been finalized at the time of filing this Annual Report on Form 10-K and the implementation of any such plan is not probable of being effectively implemented as none of the plans are entirely within the Company's control. Accordingly, substantial doubt is deemed to exist about the Company's ability to continue as a going concern within one year after the date these financial statements are issued.

If the Company is unable to obtain sufficient capital to continue to advance its programs, the Company would be forced to delay, reduce or eliminate its research and development programs and any future commercialization efforts.

The accompanying financial statements have been prepared on a going concern basis, which contemplates the realization of assets and satisfaction of liabilities in the ordinary course of business. The financial statements do not include any adjustments relating to the recoverability and classification of recorded asset amounts or the amounts and classification of liabilities that might result from the outcome of the uncertainties described above.

(2) Basis of Presentation

These consolidated financial statements include the accounts of the Company and its wholly-owned subsidiaries, AVEO Pharma Limited and AVEO Securities Corporation. The Company has eliminated all significant intercompany accounts and transactions in consolidation.

(3) Significant Accounting Policies

Revenue Recognition

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

Collaboration Arrangements Within the Scope of ASC 808, Collaborative Arrangements

The Company analyzes its collaboration arrangements to assess whether such arrangements involve joint operating activities performed by parties that are both active participants in the activities and exposed to significant risks and rewards dependent on the commercial success of such activities and are therefore within the scope of ASC Topic 808, *Collaborative Arrangements* ("ASC 808"). This assessment is performed throughout the life of the arrangement based on changes in the responsibilities of all parties in the arrangement. For collaboration arrangements that are deemed to be within the scope of ASC 808, the Company first determines which elements of the collaboration are deemed to be within the scope of ASC 808 and those that are more reflective of a vendor-customer relationship and therefore within the scope of ASC 606, *Revenue from Contracts with Customers* ("ASC 606"). The Company's policy is generally to recognize amounts received from collaborators in connection with joint operating activities that are within the scope of ASC 808 as a reduction in research and development expense.

Arrangements Within the Scope of ASC 606, Revenue from Contracts with Customers

Effective January 1, 2018, the Company adopted ASC 606 using the modified retrospective transition method. Under this method, the Company has recognized the cumulative effect of the adoption as an adjustment to the opening balance of accumulated deficit in the current period consolidated balance sheet. Financial results for the year ended December 31, 2018 are presented under ASC 606, while prior period amounts are not adjusted and continue to be reported in accordance with the Company's historical accounting under ASC 605, *Revenue Recognition*. ASC 606 applies to all contracts with customers, except for contracts that are within the scope of other standards, such as collaboration arrangements and leases.

Under ASC 606, the Company recognizes revenue when its customers obtain control of promised goods or services, in an amount that reflects the consideration which the Company determines it expects to receive in exchange for those goods or services. To determine revenue recognition for arrangements that the Company determines are within the scope of ASC 606, the Company performs the following five steps: (i) identify the contract(s) with a customer; (ii) identify the performance obligation(s) in the contract; (iii) determine the transaction price; (iv) allocate the transaction price to the performance obligation(s) in the contract; and (v) recognize revenue when (or as) the Company satisfies its performance obligation(s). As part of the accounting for these arrangements, the Company must make significant judgments, including identifying performance obligations in the contract, estimating the amount of variable consideration to include in the transaction price and allocating the transaction price to each performance obligation.

Once a contract is determined to be within the scope of ASC 606, the Company assesses the goods or services promised within the contract and determines those that are performance obligations. Arrangements that include rights to additional goods or services that are exercisable at a customer's discretion are generally considered options. The Company assesses if these options provide a material right to the customer and if so, they are considered performance obligations. The exercise of a material right is accounted for as a contract modification for accounting purposes.

The Company assesses whether each promised good or service is distinct for the purpose of identifying the performance obligations in the contract. This assessment involves subjective determinations and requires management to make judgments about the individual promised goods or services and whether such are separable from the other aspects of the contractual relationship. Promised goods and services are considered distinct provided that: (i) the customer can benefit from the good or service either on its own or together with other resources that are readily available to the customer (that is, the good or service is capable of being distinct) and (ii) the entity's promise to transfer the good or service to the customer is separately identifiable from other promises in the contract (that is, the promise to transfer the good or service is distinct within the context of the contract). In assessing whether a promised good or service is distinct, the Company considers factors such as the research, manufacturing and commercialization capabilities of the collaboration partner and the availability of the associated expertise in the general marketplace. The Company also considers the intended benefit of the contract in assessing whether a promised good or service is separately identifiable from other promises in the contract. If a promised good or service is not distinct, an entity is required to combine that good or service with other promised goods or services until it identifies a bundle of goods or services that is distinct.

The transaction price is then determined and allocated to the identified performance obligations in proportion to their standalone selling prices ("SSP") on a relative SSP basis. SSP is determined at contract inception and is not updated to reflect changes between contract inception and when the performance obligations are satisfied. Determining the SSP for performance obligations requires significant judgment. In developing the SSP for a performance obligation, the Company considers applicable market conditions and relevant entity-specific factors, including factors that were contemplated in negotiating the agreement with the customer and estimated costs. The Company validates the SSP for performance obligations by evaluating whether changes in the key assumptions used to determine the SSP will have a significant effect on the allocation of arrangement consideration between multiple performance obligations.

If the consideration promised in a contract includes a variable amount, the Company estimates the amount of consideration to which it will be entitled in exchange for transferring the promised goods or services to a customer. The Company determines the amount of variable consideration by using the expected value method or the most likely amount method. The Company includes the unconstrained amount of estimated variable consideration in the transaction price. The amount included in the transaction price is constrained to the amount for which it is probable that a significant reversal of cumulative revenue recognized will not occur. At the end of each subsequent reporting period, the Company re-evaluates the estimated variable consideration included in the transaction price and any related constraint, and if necessary, adjusts its estimate of the overall transaction price. Any such adjustments are recorded on a cumulative catch-up basis in the period of adjustment.

In determining the transaction price, the Company adjusts consideration for the effects of the time value of money if the timing of payments provides the Company with a significant benefit of financing. The Company does not assess whether a contract has a significant financing component if the expectation at contract inception is such that the period between payment by the licensees and the transfer of the promised goods or services to the licensees will be one year or less. The Company assessed each of its revenue generating arrangements in order to determine whether a significant financing component exists and concluded that a significant financing component does not exist in any of its arrangements.

The Company then recognizes as revenue the amount of the transaction price that is allocated to the respective performance obligation when (or as) each performance obligation is satisfied at a point in time or over time, and if over time based on the use of an output or input method.

Licenses of intellectual property: The terms of the Company's license agreements include the license of functional intellectual property, given the functionality of the intellectual property is not expected to change substantially as a result of the Company's ongoing activities. If the license to the Company's intellectual property is determined to be distinct from the other performance obligations identified in the arrangement, the Company recognizes revenues from the portion of the transaction price allocated to the license when the license is transferred to the licensee and the licensee is able to use and benefit from the license. For licenses that are bundled with other promises (that is, for licenses that are not distinct from other promised goods and services in an arrangement), the Company utilizes judgment to assess the nature of the combined performance obligation to determine whether the combined performance obligation is satisfied over time or at a point in time and, if over time, the appropriate method of measuring progress for purposes of recognizing revenue. The Company evaluates the measure of progress each reporting period and, if necessary, adjusts the measure of performance and related revenue recognition.

Research and development funding: Arrangements that include payment for research and development services are generally considered to have variable consideration. If and when the Company assesses the payment for these services is no longer subject to the constraint on variable consideration, the related revenue is included in the transaction price.

Milestone payments: At the inception of each arrangement that includes non-refundable payments for contingent milestones, including preclinical research and development, clinical development and regulatory, the Company evaluates whether the milestones are considered probable of being achieved and estimates the amount to be included in the transaction price using the most likely amount method. If it is probable that a significant revenue reversal would not occur, the associated milestone value is included in the transaction price. Milestone payments that are not within the control of the Company or the licensee, such as regulatory approvals, are not considered probable of being achieved until those approvals are received. At the end of each reporting period, the Company re-evaluates the probability of the achievement of contingent milestones and the likelihood of a significant reversal of such milestone revenue, and if necessary, adjusts its estimate of the overall transaction price. Any such adjustments are recorded on a cumulative catch-up basis, which would affect collaboration and licensing revenue in the period of adjustment. This quarterly assessment may result in the recognition of revenue related to a contingent milestone payment before the milestone event has been achieved.

Royalties: For arrangements that include sales-based royalties, including milestone payments based on the level of sales, and the license is deemed to be the predominant item to which the royalties relate, the Company recognizes revenue at the later of (i) when the related sales occur, or (ii) when the performance obligation to which some or all of the royalty has been allocated has been satisfied (or partially satisfied).

The following table summarizes the total revenues earned in the years ended December 31, 2018, 2017 and 2016, respectively, by partner (in thousands). Refer to Note 4 *Collaborations and License Agreements* regarding specific details.

	Years Ended December 31,		
	2018	2017	2016
Strategic Partner:	($ in thousands)		
EUSA	$ 3,409	$ 4,414	$ 395
CANbridge	2,000	1,000	1,028
Novartis	—	1,800	—
Biogen Idec	—	—	38
Pharmstandard	—	—	939
Ophthotech	—	115	115
Other	—	250	—
Total revenues	$ 5,409	$ 7,579	$ 2,515

Research and Development Expenses

Research and development expenses are charged to expense as incurred. Research and development expenses consist of costs incurred in performing research and development activities, including internal costs for salaries, bonuses, benefits, stock-based compensation, facilities, and research-related overhead, and external costs for clinical trials, drug manufacturing and distribution, license fees, consultants and other contracted services.

Warrants Issued in Connection with Private Placement

In May 2016, the Company issued warrants to purchase an aggregate of 17,642,482 shares of common stock in connection with a private placement financing and recorded the warrants as a liability (the "PIPE Warrants"). The Company accounts for warrant instruments that either conditionally or unconditionally obligate the issuer to transfer assets as liabilities regardless of the timing of the redemption feature or price, even though the underlying shares may be classified as permanent or temporary equity. As of December 31, 2018, PIPE Warrants exercisable for 803,108 shares of common stock had been exercised, for approximately $0.8 million in cash proceeds, and PIPE Warrants exercisable for 16,839,375 shares of common stock were outstanding. In July 2017, Hercules Capital Inc. exercised its PIPE Warrants with respect to all 259,067 shares of common stock underlying such PIPE Warrants, and the Company issued Hercules Capital Inc. 259,067 shares of its common stock and received approximately $0.3 million in cash proceeds. In 2018, PIPE Warrants with respect to 544,041 shares of common stock underlying such PIPE Warrants were exercised, and the Company issued 544,041 shares of its common stock and received approximately $0.5 million in cash proceeds. Refer to Note 7, "*Common Stock—Private Placement / PIPE Warrants"* for further discussion of the private placement financing.

The PIPE Warrants contain a provision giving the warrant holder the option to receive cash, equal to the fair value of the remaining unexercised portion of the warrant, as cash settlement in the event that there is a fundamental transaction (contractually defined to include various merger, acquisition or stock transfer activities). Due to this provision, ASC 480, *Distinguishing Liabilities from Equity* requires that these warrants be classified as a liability and not as equity. Accordingly, the Company recorded a warrant liability in the amount of approximately $9.3 million upon issuance of the PIPE Warrants. The fair value of these warrants has been determined using the Black-Scholes pricing model. These warrants are subject to revaluation at each balance sheet date and any changes in fair value are recorded as a non-cash gain or (loss) in the Statement of Operations as a component of other income (expense), net until the earlier of their exercise or expiration or upon the completion of a liquidation event. Upon exercise, the PIPE Warrants are subject to revaluation just prior to the date of the warrant exercise and any changes in fair value are recorded as a non-cash gain or (loss) in the Statement of Operations as a component of other income (expense), net and the corresponding reduction in the PIPE Warrant liability is recorded as additional paid-in capital in the Balance Sheet as a component of stockholder's equity.

The Company recorded a non-cash gain of approximately $19.9 million in the year ended December 31, 2018, a non-cash loss of $33.7 million in the year ended December 31, 2017 and a non-cash gain of approximately $4.8 million in the year ended December 31, 2016 in its Statement of Operations attributable to the increases and decreases in the fair value of the warrant liability that resulted from lower stock prices as of December 31, 2018, higher stock prices as of December 31, 2017 and lower stock prices as of December 31, 2016, relative to prior periods. The Company recorded a reduction in the warrant liability attributable to warrant exercises, with a corresponding increase to additional paid-in capital, of approximately $1.2 million, $0.6 million and $0 in the years ended December 31, 2018, 2017 and 2016, respectively.

The following table rolls forward the fair value of the Company's PIPE warrant liability, the fair value of which is determined by Level 3 inputs for the year ended December 31, 2018 (in thousands):

Issuance of Warrants on May 13, 2016	$	9,344
Decrease in fair value		(4,751)
Fair value at December 31, 2016	$	4,593
Increase in fair value		33,740
Reduction in warrant liability for PIPE Warrant exercises		(587)
Fair value at December 31, 2017	$	37,746
Decrease in fair value		(19,919)
Reduction in warrant liability for PIPE Warrant exercises		(1,153)
Fair value at December 31, 2018	$	16,674

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

	Original Issuance	December 31, 2016	December 31, 2017	December 31, 2018
Expected price volatility	76.25%	78.18%	84.86%	82.64%
Expected term (in years)	5.00	4.50	3.50	2.50
Risk-free interest rates	1.22%	1.93%	2.09%	2.47%
Stock price	$ 0.89	$ 0.54	$ 2.79	$ 1.60
Dividend yield	—	—	—	—

Prior Class Action Settlement and Settlement Warrants

In December 2017, the Company entered into a binding memorandum of understanding (the "MOU") with class representatives Bob Levine and William Windham (the "Plaintiffs"), regarding the settlement of a securities class action lawsuit (the "Class Action") that had been filed in 2013 and was pending in the United States District Court for the District of Massachusetts (the "District Court") against the Company and certain of the Company's former officers (Tuan Ha-Ngoc, David Johnston, and William Slichenmyer, together, the "Individual Defendants"), *In re AVEO Pharmaceuticals, Inc. Securities Litigation et al.*, No. 1:13-cv-11157-DJC. As previously disclosed, the Class Action was purportedly brought on behalf of stockholders who purchased the Company's common stock between May 16, 2012 and May 1, 2013 (the "Class").

In December 2017, upon entering into the MOU, the Company's liability related to this settlement became estimable and probable. Accordingly, the Company recorded an estimated $17.1 million contingent liability, including $15.0 million for the cash portion of the settlement with a corresponding insurance recovery for the 100% portion to be paid directly by certain of the Company's insurance carriers, and an approximate $2.1 million estimate for the fair value on December 31, 2017 of 2.0 million warrants to purchase shares of its common stock that the Company agreed to issue the Class (the "Settlement Warrants"), with a corresponding non-cash charge to the Statement of Operations as a component of operating expense. The Settlement Warrants are exercisable for a one-year period from their date of issue at an exercise price equal to the closing price on December 22, 2017, the trading day prior to the execution of the MOU, which was $3.00 per share.

The settlement was subject to the execution of a definitive settlement agreement, notice to the Class, and final approval of the District Court and became effective on the date (the "Effective Date") on which all of the following conditions occurred: (a) a final judgment containing the requisite release of claims had been entered by the District Court; (b) no appeal was pending with respect to the final judgment; (c) the final judgment had not been reversed, modified, vacated or amended; (d) the time to file any appeal from the final judgment had expired without the filing of an appeal or an order dismissing the appeal or affirming the final judgment had been entered, and any time to file a further appeal (including a writ of certiorari or for reconsideration of the appeal) had expired; and (e) the MOU and any settlement agreement with respect to the claims released in the final judgment had not expired or been terminated.

In January 2018, the Company entered into a definitive stipulation of settlement agreement (the "Stipulation"). In February 2018, the District Court preliminarily approved the Stipulation, following which the insurance carriers funded the settlement escrow account related to the $15.0 million cash portion of the settlement. On May 30, 2018, the District Court approved the Stipulation in its order of final approval and final judgment (the "Final Judgment"). Upon the conclusion of a 30-day appeal period, the Effective Date was deemed to be June 29, 2018. Pursuant to the Final Judgment, all claims against the Company were released upon the Effective Date. In addition, pursuant to the Stipulation, the Company had no interest in the settlement escrow account subsequent to the Effective Date. Accordingly, the $15.0 million contingent liability associated with the cash portion of the settlement and the corresponding insurance recovery was eliminated on the Effective Date. The Company had agreed to use its best efforts to issue and deliver the Settlement Warrants within ten business days following the Effective Date. On July 16, 2018, the Company issued and delivered the Settlement Warrants in accordance with the Stipulation and filed a corresponding shelf registration statement, File No. (333-226190) to register the shares of common stock underlying the Settlement Warrants which was declared effective by the SEC on July 25, 2018.

Refer to Note 13, "*Legal Proceedings*" for further discussion of the Class Action settlement.

The estimated fair value of the Settlement Warrants was determined using the Black-Scholes pricing model. The estimated fair value of the Settlement Warrants was subject to revaluation at each balance sheet date and any changes in fair value were recorded as a non-cash gain or (loss) in the Statement of Operations as a component of operating expenses until the Settlement Warrants were issued. The Company recorded a non-cash gain of approximately $0.7 million during the year ended December 31, 2018 in its Statement of Operations attributable to the decrease in the fair value of the Settlement Warrants from December 31, 2017 to the date the Settlement Warrants were issued that principally resulted from a lower volatility rate relative to prior periods. In July 2018, upon the issuance of the Settlement Warrants, the Company reclassified the approximate $1.4 million value of the Settlement Warrants from a liability to stockholders equity as a component of additional paid-in-capital based upon the terms of the warrant agreement and, accordingly, the approximate $1.4 million contingent liability on the Company's balance sheet associated with the warrant portion of the settlement was eliminated.

The key assumptions used to estimate the fair value the Settlement Warrants were as follows:

	December 31, 2017	June 30, 2018
Expected price volatility	101.52%	62.74%
Expected term (in years)	1.00	1.00
Risk-free interest rates	1.76%	2.37%
Stock price	$ 2.79	$ 2.90
Dividend yield	—	—

Cash and Cash Equivalents

The Company considers all highly liquid investments with original maturities of three months or less at the date of purchase and an investment in a U.S. government money market fund to be cash equivalents. Changes in the balance of cash and cash equivalents may be affected by changes in investment portfolio maturities, as well as actual cash disbursements to fund operations.

The Company's cash is deposited in highly-rated financial institutions in the United States. The Company invests in U.S. government money market funds, high-grade, short-term commercial paper, corporate bonds and other U.S. government agency securities, which management believes are subject to minimal credit and market risk. The carrying values of the Company's cash and cash equivalents approximate fair value due to their short-term maturities.

The Company does not have any restricted cash balances.

Marketable Securities

Marketable securities consist primarily of investments which have expected average maturity dates in excess of three months, but not longer than 24 months. The Company invests in high-grade corporate obligations, including commercial paper, and U.S. government and government agency obligations that are classified as available-for-sale. Since these securities are available to fund current operations they are classified as current assets on the consolidated balance sheets.

Marketable securities are stated at fair value, including accrued interest, with their unrealized gains and losses included as a component of accumulated other comprehensive income or loss, which is a separate component of stockholders' equity. The fair value of these securities is based on quoted prices and observable inputs on a recurring basis. The cost of marketable securities is adjusted for amortization of premiums and accretion of discounts to maturity, with such amortization and accretion recorded as a component of interest expense, net. Realized gains and losses are determined on the specific identification method. Unrealized gains and losses are included in other comprehensive loss until realized, at which point they would be recorded as a component of interest expense, net.

Below is a summary of cash, cash equivalents and marketable securities at December 31, 2018 and December 31, 2017:

	Amortized Cost	Unrealized Gains	Unrealized Losses	Fair Value
December 31, 2018				
Cash and cash equivalents:				
Cash and money market funds	$ 16,211	$ —	$ —	$ 16,211
Corporate debt securities	8,215	1	—	8,216
Total cash, cash equivalents and marketable securities	**$ 24,426**	**$ 1**	**$ —**	**$ 24,427**
December 31, 2017				
Cash and cash equivalents:				
Cash and money market funds	$ 14,949	$ —	$ —	$ 14,949
Corporate debt securities	—	—	—	—
Total cash and cash equivalents	14,949	—	—	14,949
Marketable securities:				
Corporate debt securities due within 1 year	$ 17,074	$ 1	$ (5)	$ 17,070
U.S. government agency securities due within 1 year	1,506	—	—	1,506
Total marketable securities	18,580	1	(5)	18,576
Total cash, cash equivalents and marketable securities	**$ 33,529**	**$ 1**	**$ (5)**	**$ 33,525**

Concentrations of Credit Risk

Financial instruments that potentially subject the Company to credit risk primarily consist of cash and cash equivalents, marketable securities and accounts receivable. The Company maintains deposits in highly-rated, federally-insured financial institutions in excess of federally insured limits. The Company's investment strategy is focused on capital preservation. The Company invests in instruments that meet the high credit quality standards outlined in the Company's investment policy. This policy also limits the amount of credit exposure to any one issue or type of instrument.

The Company's accounts receivable primarily consists of amounts due to the Company from licensees and collaborators. The Company has not experienced any material losses related to accounts receivable from individual licensees or collaborators.

Fair Value Measurements

The fair value of the Company's financial assets and liabilities reflects the Company's estimate of amounts that it would have received in connection with the sale of the assets or paid in connection with the transfer of the liabilities in an orderly transaction between market participants at the measurement date. In connection with measuring the fair value of its assets and liabilities, the Company seeks to maximize the use of observable inputs (market data obtained from sources independent from the Company) and to minimize the use of unobservable inputs (the Company's assumptions about how market participants would price assets and liabilities). The following fair value hierarchy is used to classify assets and liabilities based on the observable inputs and unobservable inputs used in order to value the assets and liabilities:

Level 1: Quoted prices in active markets for identical assets or liabilities. An active market for an asset or liability is a market in which transactions for the asset or liability occur with sufficient frequency and volume to provide pricing information on an ongoing basis.

Level 2: Observable inputs other than Level 1 inputs. Examples of Level 2 inputs include quoted prices in active markets for similar assets or liabilities and quoted prices for identical assets or liabilities in markets that are not active.

Level 3: Unobservable inputs based on the Company's assessment of the assumptions that market participants would use in pricing the asset or liability.

Financial assets and liabilities are classified in their entirety within the fair value hierarchy based on the lowest level of input that is significant to the fair value measurement. The Company measures the fair value of its marketable securities by taking into consideration valuations obtained from third-party pricing sources. The pricing services utilize industry standard valuation models, including both income and market-based approaches, for which all significant inputs are observable, either directly or indirectly, to estimate fair value. These inputs include reported trades of and broker-dealer quotes on the same or similar securities, issuer credit spreads, benchmark securities and other observable inputs.

As of December 31, 2018, the Company's financial assets valued based on Level 1 inputs consisted of cash and cash equivalents in a U.S. government money market fund and its financial assets valued based on Level 2 inputs consisted of high-grade corporate debt securities, including commercial paper. During the year ended December 31, 2018, the Company did not have any transfers of financial assets between Levels 1 and 2.

As of December 31, 2018, the Company's financial liability that was recorded at fair value consisted of the PIPE Warrant liability.

The fair value of the Company's loans payable at December 31, 2018 approximates its carrying value, computed pursuant to a discounted cash flow technique using a market interest rate and is considered a Level 3 fair value measurement. The effective interest rate, which reflects the current market rate, considers the fair value of the warrants issued in connection with the loan, loan issuance costs and the deferred financing charge.

The following table summarizes the assets and liabilities measured at fair value on a recurring basis at December 31, 2018 and December 31, 2017:

	Fair Value Measurements as of December 31, 2018			
	Level 1	Level 2	Level 3	Total
	(in thousands)			
Financial assets carried at fair value:				
Cash and money market funds	$ 16,211	$ —	$ —	$ 16,211
Corporate debt securities	—	8,216	—	8,216
Total cash, cash equivalents and marketable securities	**$ 16,211**	**$ 8,216**	**$ —**	**$ 24,427**
Financial liabilities carried at fair value:				
Total PIPE Warrant liability	**$ —**	**$ —**	**$ 16,674**	**$ 16,674**

	Fair Value Measurements as of December 31, 2017			
	Level 1	Level 2	Level 3	Total
	(in thousands)			
Financial assets carried at fair value:				
Cash and money market funds	$ 14,949	$ —	$ —	$ 14,949
Corporate debt securities	—	—	—	—
Total cash and cash equivalents	$ 14,949	$ —	$ —	$ 14,949
Marketable securities:				
Corporate debt securities due within 1 year	$ —	$ 17,070	$ —	$ 17,070
U.S. government agency securities due within 1 year	—	1,506	—	1,506
Total marketable securities	$ —	$ 18,576	$ —	$ 18,576
Total cash, cash equivalents and marketable securities	**$ 14,949**	**$ 18,576**	**$ —**	**$ 33,525**
Financial liabilities carried at fair value:				
PIPE Warrant liability	$ —	$ —	$ 37,746	$ 37,746
Settlement Warrant liability	—	—	2,073	2,073
Total warrant liabilities	**$ —**	**$ —**	**$ 39,819**	**$ 39,819**

Property and Equipment

Property and equipment are stated at cost and are depreciated using the straight-line method over the estimated useful lives of the respective assets. Maintenance and repair costs are charged to expense as incurred. Depreciation expense for the years ended December 31, 2018, 2017 and 2016 was $0, $0 and $30 thousand, respectively.

Long-lived Assets

The Company reviews long-lived assets, including property and equipment, for impairment whenever changes in business circumstances indicate that the carrying amount of the asset may not be fully recoverable. The Company recognized $0 in impairment losses during each of the years ended December 31, 2018, 2017 and 2016, respectively.

Basic and Diluted Net Loss per Common Share

Basic net loss per share attributable to AVEO common stockholders is based on the weighted-average number of common shares outstanding during the period. Diluted net loss per share attributable to AVEO common stockholders is based on the weighted-average number of common shares outstanding during the period plus additional weighted-average common equivalent shares outstanding during the period when the effect is dilutive. For the year ended December 31, 2018, common equivalent shares include the incremental common shares issuable upon the exercise of the PIPE Warrants, as determined using the treasury stock method, and exclude the incremental common shares issuable upon the exercise of the Settlement Warrants as the corresponding exercise price exceeds the average fair value of the Company's common stock during the period and their effect would be anti-dilutive. For the years ended December 31, 2017 and 2016, diluted net loss per share is the same as basic net loss per share as the inclusion of weighted-average shares of common stock issuable upon the exercise of stock options and warrants would be anti-dilutive.

The following tables summarizes the computation of basic and diluted net loss per share for the years ended December 31, 2018, 2017 and 2016, respectively (in thousands except per share amounts):

	Year Ended December 31,		
	2018	2017	2016
Basic net loss attributable to Aveo common stockholders	$ (5,329)	$ (65,025)	$ (26,887)
Less: non-cash gains attributable to the change in fair value of the PIPE warrant liability	(19,919)	—	—
Diluted net loss attributable to Aveo common stockholders	$ (25,248)	$ (65,025)	$ (26,887)
Weighted-average shares of common stock outstanding	120,592	105,930	69,268
Dilutive securities:			
Incremental common shares issuable upon the exercise of the PIPE warrants	10,138	—	—
Weighted average number of common shares outstanding and dilutive share equivalents outstanding	130,731	105,930	69,268
Basic net loss per share	$ (0.04)	$ (0.61)	$ (0.39)
Diluted net loss per share	$ (0.19)	$ (0.61)	$ (0.39)

The following table summarizes outstanding securities not included in the computation of diluted net loss per common share as their inclusion would be anti-dilutive for the years ended December 31, 2018, 2017 and 2016, respectively:

	Years Ended December 31,		
	2018	2017	2016
Options outstanding	9,583,349	7,537,958	4,858,678
PIPE Warrants outstanding	—	17,383,415	17,642,482
Settlement Warrants outstanding	2,000,000	—	—
Other warrants outstanding	—	—	1,810,813
Total	11,583,349	24,921,373	24,311,973

Stock-Based Compensation

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

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

The Company uses the Black-Scholes option pricing model to value its stock option awards without market conditions, which require the Company to make certain assumptions regarding the expected volatility of its common stock price, the expected term of the option grants, the risk-free interest rate and the dividend yield with respect to its common stock. The Company calculates volatility using its historical stock price data. Due to the lack of the Company's own historical data, the Company elected to use the "simplified" method for "plain vanilla" options to estimate the expected term of the Company's stock option grants. Under this approach, the weighted-average expected life is presumed to be the average of the vesting term and the contractual term of the option. The risk-free interest rate used for each grant is based on the U.S. Treasury yield curve in effect at the time of grant for instruments with a similar expected life. The Company utilizes a dividend yield of zero based on the fact that the Company has never paid cash dividends and has no present intention to pay cash dividends.

The fair value of equity-classified awards to employees and directors are measured at fair value on the date the awards are granted. Awards to nonemployee consultants are recorded at their fair values and are re-measured as of each balance sheet date until the recipient's services are complete. During the years ended December 31, 2018, 2017 and 2016, the Company recorded the following stock-based compensation expense (in thousands):

	Years Ended December 31,		
	2018	2017	2016
	(in thousands)		
Research and development	$ 774	$ 290	$ 293
General and administrative	1,772	799	706
Total stock-based compensation expense	$ 2,546	$ 1,089	$ 999

Stock-based compensation expense is allocated to research and development and general and administrative expenses based upon the department of the employee to whom each award was granted. No related tax benefits of the stock-based compensation expense have been recognized.

Income Taxes

The Company provides for income taxes using the asset-liability method. Under this method, deferred tax assets and liabilities are recognized based on differences between financial reporting and tax bases of assets and liabilities, and are measured using the enacted tax rates and laws that will be in effect when the differences are expected to reverse. The Company calculates its provision for income taxes on ordinary income based on its projected annual tax rate for the year. Uncertain tax positions are recognized if the position is more-likely-than-not to be sustained upon examination by a tax authority. Unrecognized tax benefits represent tax positions for which reserves have been established. The Company maintains a full valuation allowance on all deferred tax assets.

Segment and Geographic Information

Operating segments are defined as components of an enterprise engaging in business activities for which discrete financial information is available and regularly reviewed by the chief operating decision maker in deciding how to allocate resources and in assessing performance. The Company views its operations and manages its business in one operating segment principally in the United States. As of December 31, 2018, 2017 and 2016, the Company has $0, $0 and $0.8 million, respectively, of net assets located in the United Kingdom.

Use of Estimates

The preparation of financial statements in conformity with GAAP requires management to make estimates and assumptions that affect certain reported amounts of assets and liabilities, disclosure of contingent assets and liabilities at the date of the financial statements, and the reported amounts of revenues and expenses during the reporting periods. Significant items subject to such estimates and assumptions include revenue recognition, contract research accruals, measurement of the PIPE Warrant liability, estimated settlement liabilities and measurement of stock-based compensation. The Company bases its estimates on historical experience and various other assumptions that management believes to be reasonable under the circumstances. Material changes in these estimates could occur in the future. Changes in estimates are recorded in the period in which they become known. Actual results could differ from those estimates if past experience or other assumptions do not turn out to be substantially accurate.

Recently Adopted Accounting Pronouncements

In May 2014, the Financial Accounting Standards Board ("FASB") issued ASU No. 2014-09, which amends the guidance for accounting for revenue from contracts with customers. This ASU supersedes the revenue recognition requirements in ASC 605 and creates ASC 606. In 2015 and 2016, the FASB issued additional ASUs related to ASC 606 that delayed the effective date of the guidance for annual and interim periods beginning after December 15, 2017 and clarified various aspects of the new revenue guidance. ASC Topic 606 also impacts certain other areas, such as the accounting for costs to obtain or fulfill a contract, and requires disclosure of the nature, amount, timing, and uncertainty of revenue and cash flows arising from contracts with customers.

On January 1, 2018, the Company adopted ASC 606 using the modified retrospective method and applied the new guidance to the most current period presented with the cumulative effect of changes reflected in the opening balance of accumulated deficit. The Company conducted an analysis with respect to its then active revenue arrangements, which at the time included those with EUSA, CANbridge Life Sciences Ltd. ("CANbridge") and Novartis International Pharmaceutical Ltd. ("Novartis").

The adoption of ASC 606 resulted in an approximate $2.7 million increase in each of deferred revenue and the accumulated deficit at the transition date. The transition adjustment related solely to the Company's revenue arrangement with EUSA. The transition adjustment resulted from a change to the Company's accounting policy with respect to the recognition of milestone payments as a result of adopting ASC 606. Prior to the adoption of ASC 606, the Company generally recognized milestone payments in their entirety as revenue in the period the payment was earned. However, under ASC 606, milestone payments are considered to be a form of variable consideration that, upon inclusion in the transaction price, is recognized when (or as) the remaining performance obligation(s) are satisfied. Because the Company's performance obligation under the EUSA Agreement was only partially satisfied at January 1, 2018, a milestone payment received under that arrangement prior to the January 1, 2018 transition date has not been fully recognized as revenue as under ASC 606 as of the transition date.

As a result of adopting ASC 606, the Company established a deferred revenue deferred tax asset, in the amount of $0.7 million, and a corresponding offsetting valuation allowance, such that there was not tax impact on the Company's consolidated financial statements as a result of adopting ASC 606.

There was no impact from adopting ASC 606 to the Company's revenue arrangements with CANbridge and Novartis as (i) the Company did not have any unsatisfied performance obligations under the Company's collaboration and license agreement with CANbridge (the "CANbridge Agreement") and the Company's license agreement with Novartis (the "Novartis Agreement") upon the adoption of ASC 606 and (ii) the transaction price under ASC 606 as of the transition date was the same as the arrangement consideration under ASC Topic 605.

Financial results for reporting periods beginning after January 1, 2018, are presented under ASC 606, while prior period amounts are not adjusted and continue to be reported in accordance with the Company's historical accounting under ASC 605.

The following table summarizes the cumulative effect of the adoption of ASC 606 to the Company's contracts with customers that were not completed as of the January 1, 2018 transition date (in thousands):

	Impact of ASC 606 Adoption on Consolidated Balance Sheet as of January 1, 2018		
	As reported under ASC Topic 606	Adjustments	Balances without adoption of ASC Topic 606
Deferred revenue, current portion	$ 1,027	$ 632	$ 395
Deferred revenue, net of current portion	$ 3,381	$ 2,079	$ 1,302
Accumulated deficit	$ (589,680)	$ (2,711)	$ (586,969)

The following tables summarize the impact of the adoption of ASC 606 to the Company's consolidated financial statements at December 31, 2018 and for the year ended December 31, 2018 as follows (in thousands, except per share figures):

	Impact of ASC 606 Adoption on Consolidated Balance Sheet as of December 31, 2018		
	As reported under ASC Topic 606	Adjustments	Balances without adoption of ASC Topic 606
Deferred revenue, current portion	$ 1,658	$ 1,263	$ 395
Deferred revenue, net of current portion	$ 3,802	$ 2,895	$ 907
Accumulated deficit	$ (595,009)	$ (4,158)	$ (590,851)

	Impact of ASC 606 Adoption on Consolidated Statement of Operations and Comprehensive Loss		
	Year Ended December 31, 2018		
	As reported under ASC Topic 606	Adjustments	Balances without adoption of ASC Topic 606
Collaboration and licensing revenue	$ 4,947	$ (1,448)	$ 6,395
Total revenues	$ 5,409	$ (1,448)	$ 6,857
Loss before provision for income taxes	$ (5,329)	$ (1,448)	$ (3,881)
Net income (loss) - basic	$ (5,329)	$ (1,448)	$ (3,881)
Net income (loss) - diluted	$ (25,248)	$ (1,448)	$ (23,800)
Net income (loss) per share - basic	$ (0.04)	$ (0.01)	$ (0.03)
Net income (loss) per share - diluted	$ (0.19)	$ (0.01)	$ (0.18)

	Impact of ASC 606 Adoption on Consolidated Statement of Cash Flows as of December 31, 2018		
	As reported under ASC Topic 606	Adjustments	Balances without adoption of ASC Topic 606
Net loss	$ (5,329)	$ (1,448)	$ (3,881)
Changes in deferred revenue	$ 1,052	$ 1,448	$ (396)

Refer to Note 3 "*Significant Accounting Policies – Revenue Recognition*" and Note 4 "*Collaborations and License Agreements*" for further details.

In August 2016, the FASB issued ASU 2016-15, *Statement of Cash Flows (Topic 230): Classification of Certain Cash Receipts and Cash Payments*. The new standard clarifies certain aspects of the statement of cash flows, including the classification of debt prepayment or debt extinguishment costs, settlement of zero-coupon debt instruments or other debt instruments with coupon interest rates that are insignificant in relation to the effective interest rate of the borrowing, contingent consideration payments made after a business combination, proceeds from the settlement of insurance claims, proceeds from the settlement of corporate-owned life insurance policies, distributions received from equity method investees and beneficial interests in securitization transactions. The new standard also clarifies that an entity should determine each separately identifiable source or use within the cash receipts and cash payments on the basis of the nature of the underlying cash flows. In situations in which cash receipts and payments have aspects of more than one class of cash flows and cannot be separated by source or use, the appropriate classification should depend on the activity that is likely to be the predominant source or use of cash flows for the item. The Company adopted the new standard upon the required effective date of January 1, 2018. The adoption of this standard did not have a material impact on the Company's consolidated statements of cash flows.

In May 2017, the FASB issued ASU 2017-09, *Compensation-Stock Compensation (Topic 718): Scope of Modification Accounting*, which clarifies when to account for a change to the terms or conditions of a share-based payment award as a modification. The new standard does not change the accounting for modifications but clarifies that modification accounting guidance should only be applied if the fair value, vesting conditions, or classification of the award changes as a result of the change in terms or conditions. The Company adopted the new standard effective January 1, 2018. The adoption of this standard did not have a material impact on the Company's consolidated financial statements.

Pending Accounting Pronouncements

In February 2016, the FASB issued ASU 2016-02, *Leases (Topic 842)* ("ASU 2016-02"), which requires lessees to recognize a right-of-use asset and lease liability for most lease arrangements. In July 2018, the FASB issued ASU No. 2018-10, *Codification Improvement to Topic 842, Leases* ("ASU 2018-10") and ASU No. 2018-11, *Leases (Topic 842), Targeted Improvements* ("2018-11"). ASU 2018-10 made technical corrections to the new leases standard, clarifying certain inconsistencies in the guidance. ASU 2018-11 provides entities with a new transition method that allows them to use the effective date of the new leases standard as the date of initial application on transition. ASU 2016-02, as modified by ASU 2018-10 and ASU No. 2018-11 will be effective for annual reporting periods beginning after December 15, 2018 with early adoption permitted. The Company is currently evaluating the potential changes from this ASU.

In June 2018, the FASB issued ASU 2018-07, *Improvements to Nonemployee Share-Based Payment Accounting,* which simplifies the accounting for share-based payments to nonemployees by aligning it with the accounting for share-based payments to employees, with certain exceptions. The new standard is effective for annual reporting periods beginning after December 15, 2018 with early adoption permitted. The Company is currently evaluating the potential changes from this ASU.

In August 2018, the FASB issued ASU 2018-13, *Fair Value Measurement (Topic 820): Disclosure Framework-Changes to the Disclosure Requirements for Fair Value Measurement*, which modifies the disclosure requirements for fair value measurements. The new standard is effective for the Company on January 1, 2020. Early adoption is permitted. The Company currently is evaluating the impact the adoption of ASU 2018-13 may have on its disclosures.

(4) Collaborations and License Agreements

Out-License Agreements

AstraZeneca

In December 2018, the Company entered into a clinical supply agreement (the "AstraZeneca Agreement") with a wholly-owned subsidiary of AstraZeneca PLC ("AstraZeneca") to evaluate the safety and efficacy of AstraZeneca's IMFINZI (durvalumab), a human monoclonal antibody directed against programmed death-ligand 1 (PD-L1), in combination with tivozanib in first-line HCC in a phase 1/2 study. The Company 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. The Company did not incur any costs under the AstraZeneca Agreement in the year ended December 31, 2018.

CANbridge

On March 16, 2016, the Company entered into the CANbridge Agreement. Under the terms of the CANbridge Agreement, the Company granted CANbridge the exclusive right to develop, manufacture and commercialize AV-203, the Company's proprietary ErbB3 (HER3) inhibitory antibody, for the diagnosis, treatment and prevention of disease in all countries outside of North America (the "CANbridge Licensed Territory"). In addition, CANbridge has the right of first refusal if the Company determines to out-license 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.

Pursuant to the CANbridge Agreement, CANbridge made an upfront payment to the Company of $1.0 million in April 2016, net of $0.1 million of foreign withholding taxes. CANbridge also reimbursed the Company for $1.0 million of certain AV-203 manufacturing costs incurred by the Company prior to entering into the CANbridge Agreement. 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 December 2017, CANbridge filed an initial new drug ("IND") application with the China National Drug Administration ("CNDA") for a clinical study of AV-203, which CANbridge refers to as CAN017, in ESCC. In August 2018, CANbridge obtained regulatory approval of this IND application from the CNDA and, accordingly, the Company earned a $2.0 million development and regulatory milestone payment that was received from CANbridge in August 2018.

The Company is also 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, the Company is eligible to receive a tiered royalty, with a percentage range in the low double-digits, on net sales of approved licensed products. CANbridge's obligation to pay royalties for each licensed product expires on a country-by-country basis on the later of the expiration of patent rights covering such licensed product in such country, the expiration of regulatory data exclusivity in such country and ten years after the first commercial sale of such licensed product in such country.

CANbridge is obligated to use commercially reasonable efforts to develop and commercialize AV-203 in each of China, Japan, the United Kingdom, France, Italy, Spain, and Germany. CANbridge has responsibility for all activities and costs associated with the further development, manufacture and commercialization of AV-203 in the CANbridge Licensed Territory, including the clinical development of AV-203 through phase 2 proof-of-concept in ESCC, after which the Company may elect to contribute to certain worldwide development efforts.

A percentage of any milestone and royalty payments received by the Company pursuant to the CANbridge Agreement, excluding upfront and reimbursement payments, are due to Biogen Idec International GmbH ("Biogen") as a sublicensing fee under the option and license agreement between the Company and Biogen dated March 18, 2009, as amended. The $2.0 million development and regulatory milestone the Company 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.

Accounting Analysis Under ASC 606

The Company evaluated the CANbridge Agreement under ASC 606. Based on this evaluation, the Company identified the following promised goods and services at the inception of the CANbridge Agreement: the Company's grant of an exclusive license to develop and commercialize AV-203 in the CANbridge Licensed Territory, including all technical knowledge and data useful in the development and manufacture of AV-203. The Company determined that the license and know-how represented functional intellectual property. The Company concluded its promise to participate on a joint steering committee was immaterial in the context of the contract based on consideration of qualitative and quantitative factors. In making this evaluation the Company considered the specific personnel and time commitment that would be required to provide the joint steering committee services, concluding that the time commitment would be insignificant. Accordingly, the Company determined the CANbridge Agreement contained a single performance obligation related to the exclusive license to develop and commercialized AV-203 that was satisfied at the inception of the arrangement.

The Company determined that the $1.0 million in upfront consideration received upon the execution of the CANbridge Agreement in March 2016 and the $1.0 million reimbursement received in the year ended December 31, 2017 for certain manufacturing costs incurred by the Company prior to the Effective Date constituted the amount of the consideration to be included in the transaction price upon the adoption of ASC 606 on January 1, 2018 and attributed these amounts to the Company's single performance obligation. Because the Company satisfied the single performance obligation at the inception of the contract and had no remaining performance obligations, each of these amounts were recognized upon receipt. Upon adoption of ASC 606 on January 1, 2018, none of the development and regulatory milestones were included in the transaction price, as these milestone amounts were fully constrained. As part of its evaluation of the constraint, the Company considered multiple factors: (i) regulatory approvals are outside of the control of CANbridge, (ii) certain development and regulatory milestones are contingent upon the success of future clinical trials, if any, which is out of the control of CANbridge, and (iii) efforts by CANbridge. Any consideration related to development and regulatory milestones will be recognized when the corresponding milestones are no longer constrained as the Company does not have any ongoing performance obligations. Any consideration related to sales-based milestones (including royalties) will be recognized when the related sales occur as these amounts have been determined to relate predominantly to the license granted to CANbridge and therefore are recognized at the later of when the performance obligation is satisfied or the related sales occur. The Company will re-evaluate the transaction price, including its estimated variable consideration for milestones included in the transaction price and all constrained amounts, in each reporting period and as uncertain events are resolved or other changes in circumstances occur.

Previously, under ASC 605, the Company recognized the $1.0 million in upfront consideration as collaboration and licensing revenue in the first quarter of 2016 upon delivery of the exclusive license, and recognized the two $0.5 million payments by CANbridge for the reimbursement of manufacturing development activities conducted by the Company prior to the Effective Date as collaboration and licensing revenue in each of March 2017 and September 2017, respectively, as the amounts were fixed, determinable and non-refundable, and the Company did not have any further performance obligations. Accordingly, as the timing and amount of revenue recognition for the payments received from CANbridge are the same under ASC 605 and ASC 606, there was no transition adjustment required as of January 1, 2018.

In the third quarter of 2018, the Company increased the transaction price to $4.0 million to include the $2.0 million development and regulatory milestone that was earned in August 2018 for regulatory approval from the CNDA of an IND application for a clinical study of AV-203 in ESCC. Accordingly, the Company recognized the full $2.0 million amount as collaboration and licensing revenue during the year ended December 31, 2018, as the Company did not have any ongoing performance obligations under the CANbridge Agreement.

EUSA

In December 2015, the Company entered into the EUSA Agreement, under which the Company 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 (collectively, the "EUSA Licensed Territories") for all diseases and conditions in humans, excluding non-oncologic diseases or conditions of the eye.

EUSA made research and development reimbursement payments to the Company of $2.5 million upon the execution of the EUSA Agreement during the year ended December 31, 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 ongoing TiNivo trial. As a result of exercising its opt-in right, EUSA made an additional research and development reimbursement payment to the Company of $2.0 million. This $2.0 million 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. The Company is also eligible to receive an additional research and development reimbursement payment from EUSA of 50% of the total costs for the Company's TIVO-3 trial, up to $20.0 million, if EUSA elects to opt-in to that study.

The Company is entitled to receive milestone payments of $2.0 million per country upon reimbursement approval for RCC, if any, in each of France, Germany, Italy, Spain and the United Kingdom (collectively, 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 National Institute for Health and Care Excellence ("NICE") in the United Kingdom and the German Federal Association of the Statutory Health Insurances ("GKV-SV") in Germany, respectively, for the first-line treatment of RCC. Accordingly, the Company 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. The Company is 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 potentially up to $335.0 million upon EUSA's achievement of certain sales thresholds. The Company is also eligible to receive tiered double-digit royalties on net sales, if any, of licensed products in the EUSA Licensed Territories ranging from a low double digit up to mid-twenty percent depending on the level of annual net sales.

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. The Company, however, would owe KHK 30% of other, non-research and development payments it may receive from EUSA pursuant to the EUSA Agreement, including reimbursement approvals for RCC in up to five specified EU countries ("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 the Company earned in each of February 2018 and in November 2018 upon EUSA's reimbursement approval for FOTIVDA from the NICE in the United Kingdom and the GKV-SV in Germany, respectively, for the first-line treatment of RCC were subject to the 30% KHK sublicense fee, or $0.6 million, each. The Company paid the sublicense fees for EUSA's reimbursement approvals in the United Kingdom and Germany in April 2018 and in January 2019, respectively. EUSA is obligated to use commercially reasonable efforts to seek regulatory approval for and commercialize tivozanib throughout the EUSA Licensed Territories in RCC. EUSA has responsibility for all activities and costs associated with the further development, manufacture, regulatory filings and commercialization of tivozanib in the EUSA Licensed Territories.

Accounting Analysis Under ASC 606

Pursuant to ASC Topic 606, the Company identified the following promised goods and services at the inception of the EUSA Agreement: (i) the Company's grant of an exclusive license to develop and commercialize tivozanib in the EUSA Licensed Territories, including the Company's obligation to transfer all technical knowledge and data useful in the development and manufacture of tivozanib; (ii) the Company's obligation to cooperate with EUSA and support its efforts to file for marketing approval in the EUSA Licensed Territories and in its commercialization efforts, (iii) the Company's obligation to provide access to certain regulatory information resulting from the Company's ongoing development activities outside of the EUSA Licensed Territories and (iv) the Company's participation in a joint steering committee. The Company determined that the license to develop and commercialize tivozanib in the EUSA Licensed Territories was not distinct from the other promised goods and services and has accordingly accounted for these items as a single performance obligation. In reaching this conclusion, the Company concluded the remaining promises were essential to EUSA's use of the license.

The Company concluded at contract inception that EUSA's opt-in rights with respect to the TiNivo trial and the TIVO-3 trial did not represent material rights because at contract inception the Company had not yet initiated either trial and the option price (representing approximately 50% of the costs of the respective trial) was proportional to the value attributed to the EUSA Licensed Territories relative to the territorial rights retained by AVEO. Accordingly, the Company accounts for each opt-in as a separate arrangement when such opt-ins occur.

The Company evaluated the promised goods and services at the inception of the EUSA Agreement under ASC 606. Based on this evaluation, the Company determined that $6.5 million in research and development payments by EUSA, including the $2.5 million upfront consideration received upon the execution of the EUSA Agreement in December 2015 and the $4.0 million payment upon the receipt of marketing approval from the EMA for tivozanib (FOTIVDA) for the treatment of RCC in August 2017, constituted the amount of the consideration that was included in the transaction price upon the adoption of ASC 606 on January 1, 2018 and attributed this amount to the Company's single performance obligation. Upon adoption of ASC 606 on January 1, 2018, none of the remaining regulatory-related milestones were included in the transaction price as these milestone amounts were fully constrained. As part of its evaluation of the constraint, the Company considered multiple factors: (i) the remaining reimbursement and marketing approvals in RCC are outside of the control of EUSA and vary on a country-by-country basis, (ii) milestones related to the submission filings for EMA approval of tivozanib in up to three additional indications are contingent upon the success of future clinical trials in additional indications, if any, and are outside of the control of EUSA, (iii) milestones related to the marketing approval by the EMA for tivozanib in up to three additional indications are contingent upon the success of the corresponding future clinical trials, if any, and are outside of the control of EUSA, and (iv) efforts by EUSA. Any consideration related to sales-based milestones (including royalties) will be recognized when the related sales occur as these amounts have been determined to relate predominantly to the license granted to EUSA and therefore are recognized at the later of when the performance obligation is satisfied (or partially satisfied) or the related sales occur. The Company will re-evaluate the transaction price, including its estimated variable consideration for milestones included in the transaction price and all constrained amounts, in each reporting period and as uncertain events are resolved or other changes in circumstances occur.

Under ASC 606, the upfront consideration and regulatory milestones included in the transaction price are being recognized as collaboration and licensing revenue over the Company's performance period from contract execution in December 2015 through the remaining patent life of tivozanib in April 2022. Under ASC 606, upon the achievement of a regulatory milestone, the amount that represents the cumulative catch-up for the period from contract execution in December 2015 through the date of the milestone achievement is recognized as collaboration and licensing revenue, with the balance classified as deferred revenue and recognized as collaboration and licensing revenue over the remainder of the performance period through April 2022.

Previously, under ASC 605, the $2.5 million in upfront consideration was being recognized over the Company's performance period from contract execution in December 2015 through the remaining patent life of tivozanib in April 2022 and, accordingly, did not represent a change under ASC 606.

Previously, under ASC 605, the Company recognized regulatory milestones when they were achieved. Under ASC 606, milestone payments are included in the transaction price when they are no longer subject to the variable consideration constraint and, to the extent the milestone payment corresponds to a performance obligation where revenue is recognized over time, the milestone payment is recognized over the performance period.

The $4.0 million research and development reimbursement payment upon marketing approval by the EMA in RCC in August 2017 was recognized as revenue in the third quarter of 2017 in accordance with ASC 605-28, *Revenue Recognition—Milestone Method*, as the underlying milestone was considered to be substantive and, accordingly, did represent a change under ASC 606. The impact of the adoption of ASC 606 on January 1, 2018 resulted in increases of approximately $2.7 million in each of deferred revenue and the accumulated deficit. This amount represents the portion of the $4.0 million research and development reimbursement payment for marketing approval by the EMA in RCC that will be recognized over the remainder of the performance period through 2022 pursuant to the provisions of ASC 606.

In November 2017, the Company 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. The Company recognized approximately $462,000, $19,000 and $0 in revenue for sales royalties in the years ended December 31, 2018, 2017 and 2016, respectively.

In the first quarter of 2018, the Company increased the transaction price to $8.5 million to include the $2.0 million milestone for reimbursement approval from the NICE in the United Kingdom in first-line RCC that was achieved in February 2018. Accordingly, the Company recognized approximately $0.7 million in collaboration and licensing revenue for the cumulative catch-up for the period from contract execution in December 2015 through the milestone achievement in February 2018, with the approximate $1.3 million balance classified as deferred revenue that is being recognized as collaboration and licensing revenue over the remainder of the performance period through April 2022.

In the fourth quarter of 2018, the Company increased the transaction price to $10.5 million to include the $2.0 million milestone for reimbursement approval from the GKV-SV in Germany in first-line RCC that was achieved in November 2018. Accordingly, the Company recognized approximately $0.9 million in collaboration and licensing revenue for the cumulative catch-up for the period from contract execution in December 2015 through the milestone achievement in November 2018, with the approximate $1.1 million balance classified as deferred revenue that is being recognized as collaboration and licensing revenue over the remainder of the performance period through April 2022.

The Company recognized approximately $3.4 million, $4.4 million and $0.4 million, in total revenues under the EUSA Agreement in the years ended December 31, 2018, 2017 and 2016, respectively. As of December 31, 2018, there was approximately $5.5 million in total deferred revenue that will continue to be recognized as collaboration and licensing revenue, in the approximate amount of $0.4 million per quarter, over the duration of the Company's performance period through April 2022.

The following table summarizes the revenues earned in connection with the EUSA Agreement under ASC 606 for the year ended December 31, 2018 (in thousands):

Revenue Type	Date Achieved	Year Ended December 31, 2018
Collaboration and Licensing Revenue:		
Amounts in contract liabilities at the beginning of the period:		
Upfront payment	December 2015	$ 395
R&D payment - EMA approval in RCC	August 2017	632
New amounts in contract liabilities during the current period:		
Milestone - UK reimbursement approval	February 2018	960
Milestone - German reimbursement approval	November 2018	960
		$ 2,947
Partnership Royalties		462
Total		$ 3,409

The following table summarizes changes in the Company's accounts receivable and contract liabilities (deferred revenue) in connection with the EUSA Agreement for the year ended December 31, 2018 (in thousands):

Contract Assets	Beginning Balance January 1, 2018	Additions	Deductions	Ending Balance December 31, 2018
Accounts Receivable	$ 18	$ 4,462	$ (4,293)	187

				Deferred Revenue			
Contract Liabilities	Transaction Price	Date Achieved	Date Paid	Beginning Balance January 1, 2018	Additions	Deductions	Ending Balance December 31, 2018
Amounts in contract liabilities at the beginning of the period:							
Upfront payment	$ 2,500	December 2015	December 2015	$ 1,697	$ —	$ (395)	$ 1,302
R&D payment - EMA approval in RCC	4,000	August 2017	September 2017	2,711	—	(632)	2,079
New amounts in contract liabilities during the current period:							
Milestone - UK reimbursement approval	2,000	February 2018	March 2018	—	1,316	(276)	1,040
Milestone - German reimbursement approval	2,000	November 2018	December 2018	—	1,079	(40)	1,039
Total	$ 10,500			$ 4,408	$ 2,395	$ (1,343)	$ 5,460

Opt-In to the TiNivo Trial

In September 2017, EUSA elected to opt-in to co-develop the TiNivo trial. As previously described, the Company accounts for each opt-in as a separate arrangement. 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 the EUSA Licensed Territories. Upon the exercise of its opt-in right, EUSA became responsible for funding 50% of the total estimated costs of the TiNivo trial, up to $2.0 million. The Company is accounting for the joint development activities relative to the TiNivo trial as a joint risk-sharing collaboration in accordance with ASC 808 because EUSA is an active participant in the ongoing TiNivo trial and is exposed to significant risk and rewards in connection with the activity. Payments from EUSA with respect to its share of TiNivo trial development costs incurred by the Company pursuant to a joint development plan are recorded as a reduction in research and development expenses due to the joint risk-sharing nature of the activities that is not representative of a vendor-customer relationship.

The Company recognized reductions in research and development expenses of approximately $0.6 million, $0.9 million and $0 in the years ended December 31, 2018, 2017 and 2016, respectively. As of December 31, 2018, the Company had recognized approximately $1.5 million in cumulative total reductions in research and development expenses related to EUSA's approximate 50% share of the cumulative study-to-date costs. EUSA paid the $2.0 million maximum amount of cost sharing per the EUSA Agreement in advance of the completion of the trial. The remaining $0.5 million in prepaid cost sharing was classified as deferred research and development reimbursements as of December 31, 2018 and will continue to be recognized as a reduction in research and development expenses as the related TiNivo trial costs are incurred over the duration of the trial.

Novartis

In August 2015, the Company entered into the Novartis Agreement, under which the Company granted Novartis the exclusive right to develop and commercialize AV-380 and the Company's related antibodies worldwide. Novartis was responsible under the Novartis Agreement for the development, manufacture and commercialization of the Company's antibodies and any resulting approved therapeutic products. On June 29, 2018, Novartis notified the Company that it would be terminating its collaboration without cause. Effective August 28, 2018 the Company regained the rights to AV-380. Novartis' termination without cause triggered the termination of all licenses and other rights granted by the Company to Novartis with regard to the AV-380 program, and the grant by Novartis to the Company 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 the Company.

In connection with entry into the Novartis Agreement, Novartis made a non-refundable upfront payment to the Company of $15.0 million in September 2015. In December 2015, Novartis exercised an option to acquire the Company's inventory of clinical quality, AV-380 biological drug substance and reimbursed the Company approximately $3.5 million for such existing inventory. In February 2017, Novartis agreed to pay the Company $1.8 million out of its then future payment obligations, if any, to the Company under the Novartis Agreement. The funds were used to satisfy a $1.8 million time-based milestone obligation that the Company owed to St. Vincent's Hospital Sydney Limited ("St. Vincent's") in March 2017. Under the Novartis Agreement, the Company had been eligible to receive milestone payments and royalties tied to the commencement of clinical trials, to regulatory approvals and to sales of such products upon commercialization. None of the milestones set forth in the Novartis Agreement had been achieved prior to the termination of the Novartis Agreement.

In December 2018, the Company entered into an agreement with Novartis, or the AV-380 Transfer Agreement, to further establish and clarify the terms on which the AV-380 program will be returned to the Company and to support the Company's continuing development of the AV-380 program. The AV-380 Transfer Agreement provides for the continued transfer to AVEO of the AV-380 program as well as cooperation regarding the Company's future regulatory filings relating to AV-380. Novartis is also required to provide the AV-380 drug supply to the Company at no charge. Pursuant to the AV-380 Transfer Agreement, Novartis made a one-time payment to the Company of $2.3 million in January 2019, which the Company used to cover the $2.3 million time-based milestone obligation due to St. Vincent's in January 2019 under its 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 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.

Accounting Analysis Under ASC 606

The Company evaluated the Novartis Agreement under ASC 606. Based on this evaluation, the Company identified the following promised goods and services at the inception of the Novartis Agreement: the Company's grant of an exclusive, worldwide license to develop and commercialize the Product, including all technical knowledge and data useful in the development and manufacture of the Product. The Company concluded the license and know-how were functional intellectual property. The Company concluded its promise to provide 90 days of transition assistance was immaterial in the context of the contract based on consideration of qualitative and quantitative factors. In making this evaluation the Company considered the specific personnel and time commitment that would be required to provide any transition services, concluding that the time commitment would be insignificant. The Company also concluded the option to purchase AV-380 drug substance did not represent a material right as the purchase price was undiscounted and thus did not represent a performance obligation but would instead be accounted for as a separate arrangement if and when the option was exercised. Accordingly, the Company determined at inception the agreement contained a single performance obligation related to the exclusive license to develop and commercialize AV-380 that was satisfied at the inception of the arrangement.

The Company determined that the $15.0 million in upfront consideration upon the execution of the Novartis Agreement in August 2015 and the $1.8 million payment in February 2017 constituted the amount of the consideration to be included in the transaction price upon the adoption of ASC 606 on January 1, 2018 and attributed these amounts to the Company's single performance obligation. Because the Company satisfied the single performance obligation at the inception of the contract and had no remaining performance obligations, each of these amounts were recognized upon receipt. None of the clinical, development and regulatory milestones had been included in the transaction price as these milestone amounts were fully constrained.

The Company evaluated Novartis' exercise of its option to purchase AV-380 drug substance in the fourth quarter of 2015 and identified a single performance obligation related to the delivery of AV-380 drug substance. The performance obligation was satisfied in connection with Novartis' exercise of its option and thus the Company recognized the total transaction price of $3.5 million at the time the option was exercised.

Previously, under ASC 605, the Company recognized the $15.0 million in upfront consideration as collaboration and licensing revenue in the third quarter of 2015 and the $1.8 million payment in February 2017 as collaboration and licensing revenue in the first quarter of 2017 as these amounts were fixed, determinable and non-refundable, and there were no undelivered elements. Previously, under ASC 605, the Company recognized the $3.5 million purchase of the Company's inventory of clinical quality, AV-380 biological drug substance as collaboration and licensing revenue in the fourth quarter of 2015 upon the satisfaction of its performance obligation to deliver the AV-380 drug substance. Accordingly, as the timing and amount of revenue recognition for the payments received from Novartis are the same under ASC 605 and ASC 606, there was no transition adjustment required as of January 1, 2018.

In connection with the AV-380 Transfer Agreement, the $2.3 million payment due from Novartis was not considered a revenue transaction due to the effective termination of the Novartis Agreement on August 28, 2018 and was instead considered other income. The Company evaluated the return of the AV-380 drug supply and determined that the inventory was not capitalizable as future economic benefit is not probable at this time due to the AV-380 drug candidate being in the pre-clinical development stage.

Biodesix

In April 2014, the Company entered into a worldwide co-development and collaboration agreement with Biodesix (the "Biodesix Agreement") to develop and commercialize ficlatuzumab, the Company's HGF inhibitory antibody. Under the Biodesix Agreement, the Company 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 the Company perpetual, non-exclusive rights to certain intellectual property, including diagnostic data related to VeriStrat, with respect to the development and commercialization of ficlatuzumab; each license includes the right to sublicense, subject to certain exceptions. Pursuant to a joint development plan, the Company retains primary responsibility for clinical development of ficlatuzumab. In September 2016, the Company and Biodesix announced the termination of a phase 2 proof-of-concept clinical study of ficlatuzumab in which VeriStrat® was used to select clinical trial subjects (the "FOCAL" trial).

Under the Biodesix Agreement, with the exception of the costs incurred for the FOCAL trial, the Company and Biodesix are each required to contribute 50% of all clinical, regulatory, manufacturing and other costs to develop ficlatuzumab. Pursuant to the Biodesix Agreement, Biodesix was obligated to provide up to $15 million for the FOCAL trial, following which all costs of the FOCAL trial would be shared equally. In connection with the discontinuation of the FOCAL trial on October 14, 2016, the Company and Biodesix amended the Biodesix Agreement. Under the amendment, the Company agreed to share 50% of the shutdown costs for the FOCAL trial after August 1, 2016. In return for bearing these shutdown costs, the Company will be entitled to recover an agreed multiple of the additional costs borne by the Company out of any income Biodesix receives from the partnership in connection with the licensing or commercialization of ficlatuzumab. Following such recovery, the payment structure under the original Biodesix Agreement, which generally provides that the parties share equally in any costs and revenue, will resume without such modification.

In addition, the Company and Biodesix are funding 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.

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

Prior to the first commercial sale of ficlatuzumab, each party has the right to elect to discontinue participating in further development or commercialization efforts with respect to ficlatuzumab, which is referred to as an "Opt-Out". If either AVEO 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 AVEO elects to Opt-Out, it will continue to make the existing supply of ficlatuzumab available to Biodesix for the purposes of enabling Biodesix to complete the development of ficlatuzumab, and Biodesix will have the right to commercialize ficlatuzumab. After election of an Opt-Out, the non-opting out party shall have sole decision-making authority with respect to further development and commercialization of ficlatuzumab. Additionally, the Opting-Out Party shall be entitled to receive, if ficlatuzumab is successfully developed and commercialized, a royalty equal to 10% of net sales of ficlatuzumab throughout the world, if any, subject to offsets under certain circumstances.

Prior to any Opt-Out, the parties shall share equally in any payments received from a third-party licensee; provided, however, after any Opt-Out, the Opting-Out Party shall be entitled to receive only a reduced portion of such third-party payments. The agreement will remain in effect until the expiration of all payment obligations between the parties related to development and commercialization of ficlatuzumab, unless earlier terminated.

The Company is accounting for the joint development activities under the Biodesix Agreement as a joint risk-sharing collaboration in accordance with ASC 808 because Biodesix is an active participant in the ongoing development of ficlatuzumab via its participation on a joint steering committee that oversees the development plans for ficlatuzumab and is exposed to significant risk and rewards in connection with the activity based on its obligation to share in the costs, as defined above. Payments from Biodesix with respect to its share of ficlatuzumab development costs incurred by the Company pursuant to a joint development plan are recorded as a reduction in research and development expenses due to the joint risk-sharing nature of the activities that is not representative of a vendor-customer relationship.

The Company records reimbursements from Biodesix for expenses related to these trials and drug manufacturing as a reduction in research and development expense during the period that reimbursable expenses are incurred. As a result of the cost sharing provisions in the Biodesix Agreement, the Company reduced research and development expenses by approximately $0.3 million, $0.1 million and $2.5 million in the years ended December 31, 2018, 2017 and 2016, respectively. The amount due to the Company from Biodesix pursuant to the cost-sharing provision was approximately $0.2 million and $0.1 million as of December 31, 2018 and 2017, respectively. The Company received cash payments related to cost reimbursements of approximately $0.2 million and $0.8 million in the years ended December 31, 2018 and 2017, respectively.

Astellas Pharma

In February 2011, the Company, together with its wholly-owned subsidiary AVEO Pharma Limited, entered into a collaboration and license agreement (the "Astellas Agreement") with Astellas Pharma Inc. and certain of its subsidiaries (together, "Astellas"), pursuant to which the Company and Astellas intended to develop and commercialize tivozanib for the treatment of a broad range of cancers. Astellas elected to terminate the agreement effective on August 11, 2014, at which time the tivozanib rights were returned to the Company. In accordance with the Astellas Agreement, committed development costs, including the costs of completing certain tivozanib clinical development activities, continue to be shared equally.

The Company accounts for the joint development and commercialization activities in North America and Europe as a joint risk-sharing collaboration in accordance with ASC 808. Payments from Astellas with respect to Astellas' share of tivozanib development and commercialization costs incurred by the Company pursuant to the joint development plan, including the costs of completing certain tivozanib clinical development activities described in the preceding paragraph, were recorded as a reduction to research and development expense and general and administrative expense in the accompanying consolidated financial statements due to the joint risk-sharing nature of the activities in North America and Europe. The net amount due to the Company from Astellas pursuant to the cost-sharing provisions was $0.1 million at December 31, 2018.

Biogen Idec International GmbH

In March 2009, the Company entered into an exclusive option and license agreement with Biogen regarding the development and commercialization of the Company's discovery-stage ErbB3-targeted antibodies, AV-203, for the potential treatment and diagnosis of cancer and other diseases outside of North America (the "Biogen Agreement"). Under the Biogen Agreement, the Company was responsible for developing ErbB3 antibodies through completion of the first phase 2 clinical trial designed in a manner that, if successful, will generate data sufficient to support advancement to a phase 3 clinical trial.

In March 2014, the Company and Biogen amended the exclusive option and license agreement (the "Biogen Amendment"). Pursuant to the Biogen Amendment, Biogen agreed to the termination of its rights and obligations under the Biogen Agreement, including Biogen's option to (i) obtain a co-exclusive (with AVEO) worldwide license to develop and manufacture ErbB3 targeted antibodies and (ii) obtain exclusive commercialization rights to ErbB3 products in countries in the world other than North America. As a result, AVEO has worldwide rights to AV-203. Pursuant to the Biogen Amendment, the Company was obligated to use reasonable efforts to seek a collaboration partner for the purpose of funding further development and commercialization of ErbB3 targeted antibodies. The Company is also obligated to pay Biogen a percentage of milestone payments received by AVEO from future partnerships after March 28, 2016 and single digit royalty payments on net sales related to the sale of ErbB3 products, if any, up to a cumulative maximum amount of $50.0 million

In March 2016, the Company entered into a collaboration and license agreement for AV-203 with CANbridge, which satisfied its obligation to seek a collaboration partner for the purpose of funding further development and commercialization of ErbB3 targeted antibodies. The $2.0 million development and regulatory milestone the Company 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. Refer to "*—CANbridge*" within this Note 4 for a further description of that arrangement.

In-License Agreements

St. Vincent's

In July 2012, the Company entered into a license agreement with St. Vincent's, under which the Company obtained an exclusive, worldwide sublicensable right to research, develop, manufacture and commercialize products for human therapeutic, preventative and palliative applications that benefit from inhibition or decreased expression or activity of GDF15, which is also referred to as MIC-1 (the "St. Vincent's Agreement"). Under the St. Vincent's Agreement, St. Vincent's also granted the Company non-exclusive rights for certain related diagnostic products and research tools.

In order to sublicense certain necessary intellectual property rights to Novartis in August 2015, the Company amended and restated the St. Vincent's Agreement and made an additional upfront payment to St. Vincent's of $1.5 million. The Company is 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 the Company grants 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 the Company under the Novartis Agreement. These funds were used to satisfy a $1.8 million time-based milestone obligation that the Company owed to St. Vincent's in March 2017. As further described above under the heading "—Novartis", the Company 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. The Company will also be required to pay St. Vincent's tiered royalty payments equal to a low-single-digit percentage of any net sales it or its 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.

Kyowa Hakko Kirin (KHK)

In December 2006, the Company entered into a license agreement with KHK ("KHK Agreement") under which it 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. Its 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, the Company obtained exclusive rights in its 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. The Company 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, the Company is obligated to use commercially reasonable efforts to develop and commercialize tivozanib in its territory. Prior to the first anniversary of the first post-marketing approval sale of tivozanib in its territory, neither the Company nor any of its 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.

The Company has upfront, milestone and royalty payment obligations to KHK under the KHK Agreement. Upon entering into the KHK Agreement, the Company made an upfront payment in the amount of $5.0 million. In March 2010, the Company made a milestone payment to KHK in the amount of $10.0 million in connection with the dosing of the first patient in the Company's TIVO-1 trial. In December 2012, the Company made a $12.0 million milestone payment to KHK in connection with the acceptance by the FDA of the Company's 2012 NDA filing for tivozanib. Each milestone under the KHK Agreement is a one-time only payment obligation, accordingly, the Company did not owe KHK another milestone payment in connection with the dosing of the first patient in the Company's TIVO-3 trial, and would not owe a milestone payment to KHK when the Company files its anticipated NDA with the FDA following the receipt of positive TIVO-3 topline data. If the Company obtains approval for tivozanib in the United States., the Company would owe KHK a one-time milestone payment of $18.0 million, provided that the Company does not sublicense U.S. rights for tivozanib prior to obtaining a U.S. regulatory approval. If the Company 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 the Company sublicenses any of its rights to tivozanib to a third party, as it has done with EUSA, the sublicense defines the payment obligations of the sublicensee, which may vary from the milestone and royalty payment obligations under the KHK Agreement relating to rights the Company retains. The Company is required to pay KHK a fixed 30% of amounts the Company receives from its sublicensees, including upfront license fees, milestone payments and royalties, but excluding amounts the Company receives 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. The Company would, however, owe KHK 30% of other, non-research and development payments the Company 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 the Company earned in each of February 2018 and November 2018 upon EUSA's reimbursement approvals for FOTIVDA as a first-line treatment for RCC in the United Kingdom and in Germany, respectively, were subject to the 30% KHK sublicense fee, or $0.6 million each. The Company paid the sublicense fees for EUSA's reimbursement approvals in the United Kingdom and Germany in April 2018 and in January 2019, respectively.

The Company is also required to pay tiered royalty payments on net sales it makes of tivozanib in its 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. The Company's royalty payment obligations in a particular country in its 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 the Company's royalty and sublicense revenue obligations to KHK, determined on a product-by-product and country-by-country basis, unless the Company elects to terminate the KHK Agreement earlier. If the Company fails to meet its obligations under the KHK Agreement and is 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 the Company may have in tivozanib, including its regulatory filings, regulatory approvals, patents and trademarks for tivozanib.

(5) Other Accrued Liabilities

Other accrued expenses consisted of the following:

	December 31, 2018	December 31, 2017
	(in thousands)	
Professional fees	$ 798	$ 844
Compensation and benefits	1,046	1,325
Other	854	289
Total	$ 2,698	$ 2,458

(6) Loans Payable

On May 28, 2010, the Company entered into a loan and security agreement with Hercules Capital Inc. and certain of its affiliates (the "First Loan Agreement"). The First Loan Agreement was subsequently amended in March 2012 (the "2012 Amendment"), September 2014 (the "2014 Amendment") and May 2016 (the "2016 Amendment"). Amounts borrowed under the 2012 Amendment were repaid in full in 2015. In December 2017, the Company entered an amended and restated loan and security agreement (the "2017 Loan Agreement") with Hercules Funding III, LLC and Hercules Capital, Inc. (collectively "Hercules").

Pursuant to the 2014 Amendment, the Company received additional loan proceeds from Hercules in the amount of $10.0 million and was required to make an end-of-term payment of approximately $0.5 million on January 1, 2018. This payment was made on the first business day of 2018. The Company incurred approximately $0.2 million in loan issuance costs paid directly to Hercules, which were offset against the loan proceeds and are accounted for as a loan discount.

In connection with the 2014 Amendment, the Company issued warrants to the lenders to purchase up to 608,696 shares of the Company's common stock at an exercise price equal to $1.15 per share. The Company recorded the fair value of the warrants of approximately $0.4 million as stockholders' equity and as a discount to the related loan outstanding and is amortizing the value of the discount to interest expense over the term of the loan using the effective interest method. In July 2017, Hercules exercised all 608,696 warrants. Pursuant to the terms of the warrant, Hercules, at their election, exercised the warrants via a non-cash "net share issuance." The Company issued Hercules 369,297 shares of its common stock and did not receive any cash proceeds in connection with the warrant exercise.

Pursuant to the 2016 Amendment, the Company received additional loan proceeds from Hercules, in an aggregate amount of $10.0 million, in installments of $5.0 million in each of May 2016 and June 2017, which increased the aggregate outstanding principal balance under the First Loan Agreement to $20.0 million. The Company is required to make an end-of-term payment totaling $0.3 million on December 1, 2019. The Company incurred approximately $0.1 million in loan issuance costs paid directly to Hercules, which were offset against the loan proceeds and are accounted for as a loan discount. The 2016 Amendment included a financial covenant that required the Company to maintain an unrestricted cash position (defined as cash and liquid cash, including marketable securities) greater than or equal to $10.0 million through the date of completion of the Company's TIVO-3 trial, with results that were satisfactory to Hercules. Principal payments were scheduled to commence on January 1, 2018 and the loan was scheduled to mature on December 1, 2019.

In connection with the 2016 Amendment, the Company issued warrants to Hercules to purchase up to 1,202,117 shares of the Company's common stock at an exercise price equal to $0.87 per share. The Company recorded the fair value of the warrants of approximately $0.7 million as a component of stockholders' equity and as a discount to the related loan outstanding and is amortizing the value of the discount to interest expense over the term of the loan using the effective interest method. In July 2017, Hercules exercised all 1,202,117 warrants. Pursuant to the terms of the warrant, Hercules, at their election, exercised the warrants via a non-cash "net share issuance." The Company issued Hercules 846,496 shares of its common stock and did not receive any cash proceeds in connection with the warrant exercise.

In connection with the 2016 Amendment, Hercules also received an option, subject to the Company's written consent, not to be unreasonably withheld, to purchase, either with cash or through conversion of outstanding principal under the loan, up to $2.0 million of equity of the Company sold in any sale by the Company to third parties of equity securities resulting in at least $10.0 million in net cash proceeds to the Company, subject to certain exceptions.

In connection with the Company's May 2016 private placement (refer to Note 7, *"Common Stock – Private Placement / PIPE Warrants*"), Hercules purchased 259,067 units for cash proceeds of $0.2 million to the Company. This purchase was separate from the $2.0 million equity purchase option under the 2016 Amendment. Each unit in the May 2016 private placement included one share of the Company's common stock and a PIPE Warrant to purchase one share of the Company's common stock at an exercise price of $1.00 per share. In July 2017, Hercules exercised its PIPE Warrants with respect to all 259,067 shares of common stock underlying such PIPE Warrants. The Company issued Hercules 259,067 shares of its common stock and received approximately $0.3 million in cash proceeds.

In December 2017, the Company entered into the 2017 Loan Agreement to refinance the Company's existing loan facility with Hercules and to retire the $20.0 million in secured debt then-outstanding under the First Loan Agreement. Per the terms of the 2017 Loan Agreement, the new $20.0 million loan facility has a 42-month maturity from closing, no financial covenants, a lower interest rate and an interest-only period of no less than 12 months, which could be extended up to a maximum of 24 months, assuming the achievement of specified milestones relating to the development of tivozanib. Per the 2017 Loan Agreement, Hercules did not receive any additional warrants to purchase shares of the Company's common stock and no longer has the option, subject to the Company's written consent, to participate in its future equity financings up to $2.0 million through the purchase of the Company's common stock either with cash or through the conversion of outstanding principal under the loan.

The loan maturity date has been revised from December 2019 to July 2021. The Company was not required to make principal payments until February 1, 2019, at which time the Company would have been required to make 29 equal monthly payments of principal and interest, in the approximate amount of $0.8 million, through July 2021. An additional end-of-term payment of approximately $0.8 million is due on July 1, 2021, which increased the total end-of-term payments under the 2014 Amendment, 2016 Amendment and 2017 Loan Agreement to approximately $1.6 million. The end-of-term payments under the 2014 Amendment, in the approximate amount of $0.5 million, and the 2016 Amendment, in the amount of $0.3 million, continued to be due on their original due dates of January 1, 2018 and December 1, 2019, respectively. The financial covenant per the 2016 Amendment to maintain an unrestricted cash position greater than or equal to $10.0 million through the date of completion of the Company's TIVO-3 trial with results that are satisfactory to Hercules has been removed. Per the 2017 Loan Agreement, the interest rate decreased from 11.9% to 9.45%. The Company incurred approximately $0.1 million in loan issuance costs paid directly to Hercules, which are accounted for as a loan discount. The 2017 Loan Agreement was accounted for as a loan modification in accordance with ASC 470-50.

The Company must make interest payments on the principal balance of the loan each month it remains outstanding. Per annum interest is payable on the loan balance at the greater of 9.45% and an amount equal to 9.45% plus the prime rate minus 4.75%, as determined daily, provided however, that the per annum interest rate shall not exceed 15.0%. In 2018, the interest rate increased to 9.70%, 9.95% and 10.20% in June 2018, September 2018 and December 2018, respectively, due to corresponding increases in the prime rate.

The interest-only period could be extended by two 6-month deferrals of principal payments upon the achievement of specified milestones relating to the development of tivozanib, subject to confirmation by Hercules at its reasonable discretion.

In November 2018, Hercules granted the first 6-month extension of the interest-only period. Accordingly, this resulted in the deferment of principal payments until August 1, 2019, at which time the Company will be required to make 24 equal monthly payments of principal and interest, in the approximate amount of $0.9 million through July 2021. The end-of-term payments under the 2016 Amendment, in the amount of $0.3 million, and the 2017 Amendment, in the approximate amount of $0.8 million, continue to be due on their original due dates of December 1, 2019 and July 1, 2021, respectively.

The unamortized discount to be recognized over the remainder of the loan period was approximately $1.0 million and $1.5 million as of December 31, 2018 and 2017, respectively.

The loans are secured by a lien on all the Company's personal property (other than intellectual property), whether owned or acquired after the date of the First Loan Agreement. The 2017 Loan Agreement defines events of default, including the occurrence of an event that results in a material adverse effect upon the Company's business operations, properties, assets or condition (financial or otherwise), its ability to perform its obligations or upon the ability of the lenders to enforce any of their rights or remedies with respect to such obligations, or upon the collateral under the 2017 Loan Agreement, the related liens or the priority thereof. As of December 31, 2018, the Company was in compliance with all loan covenants, Hercules has not asserted any events of default and the Company does not believe that there has been a material adverse change as defined in the 2017 Loan Agreement.

The Company has determined that the risk of subjective acceleration under the material adverse events clause is remote and therefore has classified the outstanding principal in current and long-term liabilities based on the timing of scheduled principal payments.

Future minimum payments under the loans payable outstanding as of December 31, 2018 are as follows (amounts in thousands):

Year Ending December 31:	
2019	$ 6,122
2020	11,097
2021	7,308
2022	—
	24,527
Less amount representing interest	(3,437)
Less unamortized discount	(967)
Less deferred charges	(1,090)
Less loans payable current, net of discount	(3,254)
Loans payable, net of current portion and discount	$ 15,779

(7) Common Stock

As of December 31, 2018, the Company had 250,000,000 authorized shares of common stock, $0.001 par value, of which 126,484,781 shares were issued and outstanding.

Settlement Warrants

On July 16, 2018, the Company issued and delivered 2.0 million Settlement Warrants to purchase shares of its common stock for a one-year period after the date of issuance at an exercise price equal to $3.00 per share. Refer to Note 3, "*Significant Accounting Policies - Prior Class Action Settlement and Settlement Warrants*" for further discussion.

Sales Agreement with SVB Leerink

In February 2018, the Company entered into the Leerink Sales Agreement, pursuant to which the Company may issue and sell shares of its common stock from time to time up to an aggregate amount of $50.0 million, at its option, through SVB Leerink as its sales agent, with any sales of common stock through SVB Leerink being made by any method that is deemed an "at-the-market" offering as defined in Rule 415 promulgated under the Securities Act of 1933, as amended (the "Securities Act"), or in other transactions pursuant to an effective shelf registration statement on Form S-3. The Company agreed to pay SVB Leerink a commission of up to 3% of the gross proceeds of any sales of common stock pursuant to the Leerink Sales Agreement. In the fourth quarter of 2018, the Company sold 4,707,770 shares pursuant to the Leerink Sales Agreement, resulting in approximately $10.3 million in proceeds, net of commissions.

In February 2019, the Company sold 12,515,559 shares pursuant to the Leerink Sales Agreement, resulting in proceeds of approximately $7.5 million, net of commissions.

On November 30, 2017, the Company filed a shelf registration statement on Form S-3 with the SEC, which covers the offering, issuance and sale of up to $200.0 million of its common stock, preferred stock, debt securities, warrants and/or units (the "2017 Shelf"). The 2017 Shelf (File No. 333-221873) was declared effective by the SEC on December 15, 2017 and was filed to replace the Company's then existing shelf registration statement, which was terminated.

Public Offering – August 2018

On August 21, 2018, the Company closed an underwritten public offering of 2,500,000 shares of its common stock at the public offering price of $2.26 per share for gross proceeds of approximately $5.7 million. Two greater than 5% stockholders, including an entity affiliated with New Enterprise Associates and another stockholder purchased approximately 2,000,000 shares in this offering at the same public offering price per share as the other investors. The net offering proceeds to the Company were approximately $5.1 million after deducting underwriting discounts and estimated offering expenses payable by the Company.

Public Offering – March 2017

On March 31, 2017, the Company closed an underwritten public offering of 34,500,000 shares of its common stock, including the exercise in full by the underwriter of its option to purchase 4,500,000 shares, at the public offering price of $0.50 per share for gross proceeds of approximately $17.3 million. Certain of the Company's executive officers and a director purchased an aggregate of 420,000 shares and an entity affiliated with New Enterprise Associates purchased 6,000,000 shares in this offering at the same public offering price per share as the other investors. The net offering proceeds to the Company were approximately $15.4 million after deducting underwriting discounts and estimated offering expenses payable by the Company.

Private Placement / PIPE Warrants

In May 2016, the Company entered into a securities purchase agreement with a select group of qualified institutional buyers, institutional accredited investors and accredited investors pursuant to which the Company sold 17,642,482 units, at a price of $0.965 per unit, for gross proceeds of approximately $17.0 million. Each unit consisted of one share of the Company's common stock and a warrant to purchase one share of the Company's common stock (the "PIPE Warrants"). The PIPE Warrants have an exercise price of $1.00 per share and are exercisable for a period of five years from the date of issuance. Certain of the Company's directors and executive officers purchased an aggregate of 544,039 units in this offering at the same price as the other investors. The net offering proceeds to the Company were approximately $15.4 million after deducting placement agent fees and other offering expenses payable by the Company. As of December 31, 2018, PIPE Warrants exercisable for 803,108 shares of common stock had been exercised, for approximately $0.8 million in cash proceeds, and PIPE Warrants exercisable for 16,839,375` shares of common stock were outstanding. In July 2017, Hercules exercised its PIPE Warrants with respect to all 259,067 shares of common stock underlying such PIPE Warrants, and the Company issued Hercules 259,067 shares of its common stock and received approximately $0.3 million in cash proceeds. In 2018, PIPE Warrants with respect to 544,041 shares of common stock underlying such PIPE Warrants were exercised, and the Company issued 544,041 shares of its common stock and received approximately $0.5 million in cash proceeds.

Sales Agreement with FBR

In February 2015, the Company entered into a sales agreement (the "FBR Sales Agreement") with FBR & Co. and MLV & Co. (together "FBR"), pursuant to which the Company could issue and sell shares of its common stock from time to time up to an aggregate amount of $17.9 million, at the Company's option, through FBR as its sales agent, with any sales of common stock through FBR being made by any method that is deemed an "at-the-market" offering as defined in Rule 415 promulgated under the Securities Act or in other transactions pursuant to an effective shelf registration statement on Form S-3. The Company agreed to pay FBR a commission of up to 3% of the gross proceeds of any sales of common stock pursuant to the FBR Sales Agreement.

In June 2017, the Company conducted its final transaction under the FBR Sales Agreement and sold approximately 6.5 million shares pursuant to the FBR Sales Agreement, as amended, resulting in proceeds of approximately $8.8 million, net of commissions and issuance costs. The FBR Sales Agreement has expired.

(8) Stock-based Compensation

Stock Incentive Plan

The Company maintains the 2010 Stock Incentive Plan (the "Plan") for employees, consultants, advisors, and directors, as amended in March 2013, June 2014 and June 2017. The Plan provides for the grant of equity awards such as stock options and restricted stock. In June 2017, the Company amended the Plan to increase the total number of shares reserved under the Plan by 3,500,000 from 8,500,000 shares to 12,000,000 shares. The amendment was adopted by the Board of Directors in February 2017 and approved by stockholders at the Annual Meeting of Stockholders held on June 21, 2017. The Plan provides that the exercise price of incentive stock options cannot be less than 100% of the fair market value of the common stock on the date of the award for participants who own less than 10% of the total combined voting power of stock of the Company and not less than 110% for participants who own more than 10% of the total combined voting power of the stock of the Company. Options and restricted stock granted under the Plan vest over periods as determined by the Board, which generally are equal to four years. Options generally expire ten years from the date of grant. As of December 31, 2018, there were 1,105,666 shares of common stock available for future issuance under the Plan.

The following table summarizes stock option activity during the year ended December 31, 2018:

	Options	Weighted-Average Exercise Price	Weighted-Average Remaining Contractual Term	Aggregate Intrinsic Value
Outstanding at January 1, 2018	7,537,958	$ 2.00		
Granted	2,680,115	$ 3.03		
Exercised	(399,656)	$ 1.20		
Forfeited	(235,068)	$ 3.71		
Outstanding at December 31, 2018	9,583,349	$ 2.28	7.51	$ 3,509,000
Exercisable at December 31, 2018	5,329,326	$ 2.28	6.71	$ 2,397,000

Stock options to purchase 488,626 shares of common stock contain performance-based milestone conditions, which were not deemed probable of vesting at December 31, 2018.

The aggregate intrinsic value is based upon the Company's closing stock price of $1.60 on December 31, 2018.

The fair value of stock options subject only to service or performance conditions that are granted to employees is estimated on the date of grant using the Black-Scholes option-pricing model using the assumptions noted in the following table:

	Years Ended December 31,		
	2018	2017	2016
Volatility factor	80.18% - 83.61%	71.82% - 80.15%	72.18% - 74.47%
Expected term (in years)	5.50 - 6.25	5.50 - 6.25	3.00 - 6.25
Risk-free interest rates	2.64% - 3.10%	1.84% - 2.22%	1.07% - 2.01%
Dividend yield	—	—	—

The risk-free interest rate is determined based upon the United States Treasury's rates for U.S. Treasury zero-coupon bonds with maturities similar to those of the expected term of the options being valued. The Company does not expect to pay dividends in the foreseeable future.

In July 2016, the Company began calculating volatility using its historical data. Previously, the Company did not have sufficient history to support a calculation of volatility using only its historical data. As such, prior to July 2016, the Company used a weighted-average volatility considering the Company's own volatility since March 2010 and the volatilities of several peer companies. For purposes of identifying similar entities, the Company considered characteristics such as industry, length of trading history, similar vesting terms and in-the-money option status. Due to lack of available option activity data, the Company elected to use the "simplified" method for "plain vanilla" options to estimate the expected term of the stock option grants. Under this approach, the weighted-average expected life is presumed to be the average of the vesting term and the contractual term of the option. Based upon these assumptions, the weighted-average grant date fair value of stock options granted was $2.14, $0.97 and $0.65 during the years ended December 31, 2018, 2017 and 2016, respectively.

On January 1, 2017, the Company adopted ASU No. 2016-09, *Compensation–Stock Compensation (Topic 718): Improvements to Employee Share-Based Payment Accounting* and elected to account for forfeitures as they occur. Prior to 2017, the Company included an estimate of the value of the awards that would be forfeited in calculating compensation costs, which the Company estimated based upon actual historical forfeitures.

As of December 31, 2018, there was $5.8 million of total unrecognized stock-based compensation expense related to stock options granted to employees under the Plan. The expense is expected to be recognized over a weighted-average period of 2.5 years. The intrinsic value of options exercised was $0.4 million, $46,000 and $6,000 in the years ended December 31, 2018, 2017 and 2016, respectively.

Stock Incentive Plan—Restricted Stock

The Company periodically grants awards of restricted stock to employees. These awards typically vest upon completion of the requisite service period or upon achievement of specified performance targets.

The fair value of restricted stock awards that vested was $0, $0 and $0.1 million in the years ended December 31, 2018, 2017 and 2016, respectively.

Employee Stock Purchase Plan

In February 2010, the Board of Directors adopted the 2010 Employee Stock Purchase Plan (the "ESPP") pursuant to which the Company may sell up to an aggregate of 250,000 shares of Common Stock, as amended in March 2013. The ESPP allows eligible employees to purchase common stock at a price per share equal to 85% of the lower of the fair market value of the common stock at the beginning or end of each six-month period during the term of the ESPP. The Company has reserved 764,000 shares of common stock under the ESPP. As of December 31, 2018, there were 298,308 shares available for future issuance under the ESPP.

Pursuant to the ESPP, the Company sold a total of 8,974 shares of common stock during the year ended December 31, 2018 at purchases prices of $1.88 and $1.76, respectively, which represents 85% of the closing price of the Company's common stock on May 31, 2018 and November 30, 2018, respectively. The Company did not sell any shares of common stock during the years ended December 31, 2017 and December 31, 2016. The total stock-based compensation expense recorded as a result of the ESPP was approximately $8 thousand, $3 thousand and $2 thousand during the years ended December 31, 2018, 2017 and 2016, respectively.

(9) Commitments and Contingencies

Operating Leases

The Company leases office space under a month-to-month lease. Rent expense under the operating leases amounted to $0.7 million, $0.6 million and $0.6 million for the years ended December 31, 2018, 2017 and 2016, respectively.

Employment Agreements

Certain key executives are covered by severance and change in control agreements. Under these agreements, if the executive's employment is terminated without cause or if the executive terminates his employment for good reason, such executive will be entitled to receive severance equal to his base salary, benefits and prorated bonuses for a period of time equal to either 12 months or 18 months, depending on the terms of such executive's individual agreement. In addition, in December 2007, the Company approved a key employee change in control severance benefits plan, which was amended in November 2009, and which provides for severance and other benefits under certain qualifying termination events upon a change in control for a period of time ranging from 6 months to 18 months, depending upon the position of the key employee.

(10) Income Taxes

The Company accounts for income taxes under the provisions of ASC 740. The Company recorded a $0 and $0.1 million tax provision for the years ended December 31, 2018 and 2017, respectively. The tax provision for the period ending December 31, 2017 related to foreign withholding taxes in connection with the $1.0 million in reimbursement payments made by CANbridge in 2017 related to manufacturing development activities conducted by the Company prior to the Effective Date of the collaboration and license agreement. For the year ended December 31, 2018, the Company did not have any federal, state, or foreign income tax expense as it generated taxable losses in all filing jurisdictions.

A reconciliation of the expected income tax benefit computed using the federal statutory income tax rate to the Company's effective income tax rate is as follows for the years ended December 31, 2018, 2017 and 2016:

	Years Ended December 31,		
	2018	2017	2016
Income tax computed at federal statutory tax rate	21.0%	34.0%	34.0%
State taxes, net of federal benefit	27.2%	5.3%	5.2%
Research and development credits	5.2%	0.4%	1.4%
Other permanent differences	75.0%	(20.8)%	6.1%
Foreign rate differential	—	—	(0.1)%
Foreign withholding taxes	—	(0.2)%	(0.4)%
Tax reform - rate change	—	(97.5)%	—
Other	(2.0)%	0.1%	(6.6)%
Change in valuation allowance	(126.4)%	78.7%	(39.6)%
Total	—	—	—

With limited exceptions, the Company has incurred net operating losses from inception. At December 31, 2018, the Company had domestic federal, state, and United Kingdom (UK) net operating loss carryforwards of approximately $527.3 million, $418.0 million, and $6.0 million respectively, available to reduce future taxable income. The federal net operating loss carryforwards expire beginning in 2022 and continue through 2037 and the state loss carryforwards begin to expire in 2030 and continue through 2038. The

Company's federal net operating losses include $24.7 million, which do not expire. The foreign net operating loss carryforwards in the UK do not expire. The Company also had federal and state research and development tax credit carryforwards of approximately $10.9 million and $4.3 million, respectively, available to reduce future tax liabilities and which expire at various dates. The federal credits expire beginning in 2023 through 2038 and the state credits expire beginning in 2020 through 2033. The net operating loss and research and development carryforwards are subject to review and possible adjustment by the Internal Revenue Service and may be limited in the event of certain changes in the ownership interest of significant stockholders.

The Company's net deferred tax assets as of December 31, 2018 and 2017 are as follows (in thousands):

	December 31,	
	2018	2017
	(in thousands)	
Deferred tax assets:		
NOL carryforwards	$ 138,175	$ 131,683
Research and development credits	14,268	13,913
Deferred revenue and R&D reimbursements	1,616	770
Estimated settlement liability	384	4,664
Other temporary differences	4,383	4,420
Total deferred tax assets:	158,826	155,450
Deferred tax liabilities:		
Insurance recovery	—	(4,098)
Total deferred tax liabilities:	$ —	(4,098)
Valuation allowance	(158,826)	(151,352)
Total	$ —	$ —

A full valuation allowance has been recorded in the accompanying consolidated financial statements to offset these deferred tax assets because the future realizability of such assets is uncertain. This determination is based primarily on the Company's historical losses. Accordingly, future favorable adjustments to the valuation allowance may be required, if and when circumstances change. The valuation allowance increased by $7.5 million and $10.6 million during the years ended December 31, 2018 and 2016, respectively, which was primarily due to the generation of net operating losses. The valuation allowance decreased by $49.6 million during the year ended December 31, 2017 primarily due to "The Tax Cuts and Jobs Act" (the "Act"), which reduced the federal tax rate from 35% to 21%.

As of December 31, 2017, the Company had federal and state net operating losses of approximately $4.1 million related to excess tax deductions that had been excluded from the above table. The benefit of these net operating losses would have been recognized as an increase in additional paid in capital when it resulted in a reduction of taxes payable. In January 2017, the Company adopted ASU 2016-09, *Improvements to Employee Share-Based Payment Accounting*. As part of the adoption, the Company recorded through retained earnings these additional deferred tax assets of $4.1 million related to previously unrecognized tax losses with an equal and offsetting adjustment to the Company's valuation allowance. The net impact of the adoption on the Company's deferred tax assets was $0.

On December 22, 2017, President Trump signed into law the Act. The Act, among other things, contains significant changes to corporate taxation, including reduction of the corporate tax rate from a top marginal rate of 35% to a flat rate of 21%, limitation of the tax deduction for interest expense to 30% of adjusted earnings (except for certain small businesses), limitation of the deduction for net operating losses to 80% of current year taxable income and elimination of net operating loss carrybacks, one-time taxation of offshore earnings at reduced rates regardless of whether they are repatriated, elimination of U.S. tax on foreign earnings (subject to certain important exceptions), immediate deductions for certain new investments instead of deductions for depreciation expense over time, and modifying or repealing many business deductions and credits.

The Company recognizes the changes in tax law, including the Act, in the period the law is enacted. Accordingly, the effects of the Act have been recognized in the financial statements for the year ended December 31, 2017. As a result of the change in law, the Company recorded a reduction to its deferred tax assets of $63.3 million and a corresponding reduction to its valuation allowance. As a result, there was no impact to the Company's income statement due to the reduction in the U.S. corporate tax rate.

The Company applies FASB Interpretation No. 48, "*Accounting for Uncertainty in Income Taxes, an interpretation of FAS 109*" (codified within ASC 740, *Income Taxes*), for the financial statement recognition, measurement, presentation and disclosure of uncertain tax positions taken or expected to be taken in income tax returns. Unrecognized tax benefits represent tax positions for which reserves have been established. A full valuation allowance has been provided against the Company's deferred tax assets, so that the effect of the unrecognized tax benefits is to reduce the gross amount of the deferred tax asset and the corresponding valuation allowance. Since the Company has incurred net operating losses since inception, it has never been subject to a revenue agent review. The Company is currently open to examination under the statute of limitations by the Internal Revenue Service and state jurisdictions for the tax years ended 2015 through 2018. Carryforward tax attributes generated in years past may still be adjusted upon future examination if they have or will be used in a future period. The Company is currently not under examination by the Internal Revenue Service or any other jurisdictions for any tax years.

The Company may from time to time be assessed interest or penalties by major tax jurisdictions. The Company recognizes interest and penalties related to uncertain tax positions in income tax expense. No interest and penalties have been recognized by the Company to date.

The Company anticipates that the amount of unrecognized tax benefits recorded will not change in the next twelve months.

The following is a reconciliation of the Company's gross uncertain tax positions at December 31, 2018, 2017 and 2016:

	Years Ended December 31,		
	2018	2017	2016
	(in thousands)		
Amount established upon adoption	$ 1,200	$ 1,200	$ 1,200
Additions for current year tax provisions	—	—	—
Additions for prior year tax provisions	—	—	—
Reductions of prior year tax provisions	—	—	—
Balance as of end of year	$ 1,200	$ 1,200	$ 1,200

(11) Employee Benefit Plan

In 2002, the Company established the AVEO Pharmaceuticals, Inc. 401(k) Plan (the "401(k) Plan") for its employees, which is designed to be qualified under Section 401(k) of the Internal Revenue Code. Eligible employees are permitted to contribute to the 401(k) Plan within statutory and 401(k) Plan limits. The Company makes matching contributions of 50% of the first 5% of employee contributions. The Company made matching contributions of $0.1 million for each of the years ended December 31, 2018, 2017 and 2016.

(12) Quarterly Results (Unaudited)

	Three Month Ended			
	March 31, 2018	June 30, 2018	September 30, 2018	December 31, 2018
	(in thousands, expect per share data) (unaudited)			
Revenues	$ 1,026	$ 433	$ 2,467	$ 1,483
Operating expenses	8,056	7,005	7,879	7,826
Loss from operations	(7,030)	(6,572)	(5,412)	(6,343)
Change in fair value of PIPE Warrant liability	(1,465)	11,125	(16,172)	26,431
Other income (expense), net	(493)	(549)	(579)	1,730
Provision for income taxes	—	—	—	—
Net income (loss)	$ (8,988)	$ 4,004	$ (22,163)	$ 21,818
Basic net income (loss) per share				
Net income (loss) per share	$ (0.08)	$ 0.03	$ (0.18)	$ 0.18
Weighted average number of common shares outstanding	118,840	118,940	120,138	124,395
Diluted net income (loss) per share				
Net income (loss) per share	$ (0.08)	$ (0.06)	$ (0.18)	$ (0.03)
Weighted average number of common shares and dilutive common share equivalents outstanding	118,840	128,692	120,138	133,580

	Three Month Ended			
	March 31, 2017	June 30, 2017	September 30, 2017	December 31, 2017
	(in thousands, expect per share data) (unaudited)			
Revenues	$ 2,532	$ 351	$ 4,614	$ 82
Operating expenses	10,287	9,183	6,767	10,153
Loss from operations	(7,755)	(8,832)	(2,153)	(10,071)
Change in fair value of PIPE Warrant liability	(484)	(23,925)	(23,538)	14,207
Other expense, net	(551)	(530)	(655)	(637)
Provision for income taxes	(50)	—	(51)	—
Net income (loss)	$ (8,840)	$ (33,287)	$ (26,397)	$ 3,499
Basic net income (loss) per share				
Net income (loss) per share	$ (0.12)	$ (0.30)	$ (0.22)	$ 0.03
Weighted average number of common shares outstanding	76,246	110,550	118,006	118,323
Diluted net income (loss) per share				
Net income (loss) per share	$ (0.12)	$ (0.30)	$ (0.22)	$ (0.08)
Weighted average number of common shares and dilutive common share equivalents outstanding	76,246	110,550	118,006	130,108

(13) Legal Proceedings

On February 25, 2019, a class action lawsuit was filed against the Company and certain of its present officers and a former officer, Michael Bailey, Matthew Dallas, and Keith Ehrlich, in the Southern District of New York for the District of New York, captioned *David Hackel v. AVEO Pharmaceuticals, Inc., et al*, No. 1:19-cv-01722-AT. The complaint purports to be brought on behalf of shareholders who purchased the Company's common stock between August 4, 2016 through January 31, 2019. The complaint generally alleges that the Company and the officers violated Sections 10(b) and/or 20(a) of the Securities Exchange Act of 1934 and Rule 10b-5 promulgated thereunder by making allegedly false and/or misleading statements 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. The Company denies any allegations of wrongdoing and intends to vigorously defend against this lawsuit. However, there is no assurance that the Company will be successful in its defense or that insurance will be available or adequate to fund any settlement or judgment or the litigation costs of the action. Moreover, the Company is unable to predict the outcome or reasonably estimate a range of possible loss at this time.

In June 2018, the Company settled a consolidated class action lawsuit (the "Class Action"), *In re AVEO Pharmaceuticals, Inc. Securities Litigation et al., No. 1:13-cv-11157-DJC*, that had been filed in 2013 against the Company and certain of its former officers (Tuan Ha-Ngoc, David N. Johnston, William Slichenmyer, and Ronald DePinho) in the United States District Court for the District of Massachusetts (the "District Court"). The Class Action had been dismissed without prejudice in March 2015, and the lead plaintiffs then filed a second amended complaint bringing similar allegations, but which no longer named Mr. DePinho as a defendant. The Company moved to dismiss again, and the District Court ruled in the Company's favor and dismissed the second amended complaint with prejudice in November 2015. The lead plaintiffs appealed the District Court's decision and also filed a motion to vacate and reconsider the District Court's judgment. In January 2017, the District Court granted the plaintiffs' motion to vacate the dismissal and judgment. In February 2017, the plaintiffs filed a third amended complaint, on behalf of stockholders who purchased common stock between May 16, 2012 and May 1, 2013 (the "Class") alleging claims similar to those alleged in the prior complaints, namely that the Company and certain of the Company's former officers and directors violated Sections 10(b) and/or 20(a) of the Exchange Act and Rule 10b-5 promulgated thereunder by making allegedly false and/or misleading statements concerning the phase 3 trial design and results for the Company's TIVO-1 clinical trial in an effort to lead investors to believe that the drug would receive approval from the FDA. In July 2017, the District Court entered an order referring the case to alternative dispute resolution. The parties mediated during the fall of 2017.

On December 26, 2017, the parties entered into a binding memorandum of understanding (the "MOU") to settle the Class Action. Under the terms of the MOU, the Company agreed to cause certain of the Company's and the individual defendants' insurance carriers to provide the Class with a cash payment of $15.0 million, which included the cash amount of any attorneys' fees or litigation expenses that the District Court may award. Additionally, the Company agreed to issue to the Class the Settlement Warrants, for the purchase of 2.0 million shares of the Company's common stock, which, subject to certain conditions, are exercisable from the date of issue until the expiration of a one-year period after the date of issue at an exercise price of $3.00 per share, equal to the closing price on December 22, 2017, the trading day prior to the execution of the MOU. On January 29, 2018, the parties entered into a definitive Stipulation of Settlement (the "Stipulation"), which was filed with the District Court on February 2, 2018. On February 8, 2018, the District Court issued an order preliminarily approving the terms of the Stipulation. In February 2018, the insurance carriers funded the settlement escrow account for the $15.0 million cash settlement. On May 30, 2018, the District Court held the Final Approval Hearing and approved the settlement and the plaintiffs' request for attorneys' fees and expenses, subject to the Final Judgment. Upon the conclusion of a standard 30-day appeal period, the Effective Date was deemed to be June 29, 2018. On July 16, 2018, the Company issued and delivered the Settlement Warrants in accordance with the Stipulation and filed a corresponding shelf registration statement to register the shares of common stock underlying the Settlement Warrants which was declared effective by the SEC on July 25, 2018.

The Company evaluates developments in legal proceedings on a quarterly basis. The Company records an accrual for loss contingencies to the extent that the Company concludes that it is probable that a liability has been incurred and the amount of the related loss can be reasonably estimated. In December 2017, upon entering into the MOU, the Company's liability related to this settlement became estimable and probable. Accordingly, the Company recorded an estimated $17.1 million contingent liability, including $15.0 million for the cash portion of the settlement with a corresponding insurance recovery for the 100% portion to be paid directly by certain of the Company's insurance carriers, and an approximate $2.1 million estimate for the warrant portion of the settlement with a corresponding non-cash charge to the Statement of Operations as a component of operating expenses. Pursuant to the Final Judgment, all claims against the Company were released upon the Effective Date. In addition, pursuant to the Stipulation, the Company has no interest in the settlement escrow account subsequent to the Effective Date. Accordingly, the Company reversed the $15.0 million cash portion of the settlement from both the contingent liability and the corresponding insurance recovery as of the Effective Date. Refer to Note 3, "*Significant Accounting Policies – Prior Class Action Settlement and Settlement Warrants*" for further discussion.

In 2013, the SEC also served a subpoena on the Company for documents and information concerning tivozanib, including related communications with the FDA, investors and others. In September 2015, the SEC invited the Company to discuss the settlement of potential claims asserting that the Company violated federal securities laws by omitting to disclose to investors the recommendation by the staff of the FDA on May 11, 2012, that the Company conduct an additional clinical trial with respect to tivozanib. On March 29, 2016, the SEC filed a complaint against the Company and three of its former officers in the District Court alleging that the Company misled investors about its efforts to obtain FDA approval for tivozanib. Without admitting or denying the allegations in the SEC's complaint, the Company consented to the entry of a final judgment pursuant to which the Company paid the SEC a $4.0 million civil penalty to settle the SEC's claims against it. As this settlement was probable and estimable as of December 31, 2015, the Company recorded an estimated settlement liability of $4.0 million and recorded a corresponding loss in the Statement of Operations as a component of operating expenses. On March 31, 2016, the District Court entered a final judgment which (i) approved the settlement; (ii) permanently enjoined the Company from violating Section 17(a) of the Securities Act of 1933, as amended, Sections 10(b) and 13(a) of the Exchange Act and rules 10b-5, 12b-20, 13a-1, 13a-11 and 13a-13 promulgated thereunder; and (iii) ordered the Company to pay the agreed-to civil penalty. On September 15, 2017 and October 31, 2017, respectively, two of the Company's former officers consented to entry of final judgment to settle the SEC's claims against them. The Company is not a party to the litigation between the SEC and the remaining former officer, and the Company can make no assurance regarding the outcome of that action or the SEC's claims against that individual.

ITEM 9. Changes in and Disagreements with Accountants on Accounting and Financial Disclosure

None.

ITEM 9A. Controls and Procedures

Evaluation of Disclosure Controls and Procedures

Our management, with the participation of our Chief Executive Officer and Chief Financial Officer, evaluated the effectiveness of our disclosure controls and procedures (as defined in Rules 13a-15(e) and 15d-15(e) promulgated under the Exchange Act) as of December 31, 2018. In designing and evaluating our disclosure controls and procedures, management recognized that any controls and procedures, no matter how well designed and operated, can provide only reasonable assurance of achieving their objectives and our management necessarily applied its judgment in evaluating the cost-benefit relationship of possible controls and procedures. Based on this evaluation, our Chief Executive Officer and Chief Financial Officer concluded that our disclosure controls and procedures were (1) designed to ensure that material information relating to us is made known to our management including our principal executive officer and principal financial officer by others, particularly during the period in which this report was prepared and (2) effective, in that they provide reasonable assurance that information required to be disclosed by us in the reports the Company files or submit under the Exchange Act is recorded, processed, summarized and reported within the time periods specified in the SEC's rules and forms.

Management's report on the Company's internal control over financial reporting (as defined in Rules 13a-15(f) and 15d-15(f) under the Exchange Act) appears below.

Internal Control Over Financial Reporting

(a) Management's Report on Internal Control Over Financial Reporting

Our management is responsible for establishing and maintaining adequate internal control over financial reporting. Internal control over financial reporting is defined in Rules 13a-15(f) and 15d-15(f) promulgated under the Exchange Act as a process designed by, or under the supervision of, the company's principal executive and principal financial officers and effected by the company's board of directors, management and other personnel, to provide reasonable assurance regarding the reliability of financial reporting and the preparation of financial statements for external purposes in accordance with generally accepted accounting principles and includes those policies and procedures that:

- Pertain to the maintenance of records that in reasonable detail accurately and fairly reflect the transactions and dispositions of the assets of the company;
- Provide reasonable assurance that transactions are recorded as necessary to permit preparation of financial statements in accordance with generally accepted accounting principles, and that receipts and expenditures of the company are being made only in accordance with authorizations of management and directors of the company; and
- Provide reasonable assurance regarding prevention or timely detection of unauthorized acquisition, use or disposition of the company's assets that could have a material effect on the financial statements.

Because of its inherent limitations, internal control over financial reporting may not prevent or detect misstatements. Therefore, even those systems determined to be effective can provide only reasonable assurance with respect to financial statement preparation and presentation. Projections of any evaluation of effectiveness to future periods are subject to the risk that controls may become inadequate because of changes in conditions, or that the degree of compliance with the policies or procedures may deteriorate.

Our management assessed the effectiveness of our internal control over financial reporting as of December 31, 2018. In making this assessment, management used the criteria set forth by the Committee of Sponsoring Organizations of the Treadway Commission (COSO) in *Internal Control—Integrated Framework* (2013 framework). Based on its assessment, management believes that, as of December 31, 2018, our internal control over financial reporting was effective based on those criteria.

Our independent registered public accounting firm has issued an attestation report of our internal control over financial reporting. This report appears below.

(b) Report of Independent Registered Public Accounting Firm

To the Stockholders and the Board of Directors of AVEO Pharmaceuticals, Inc.

Opinion on Internal Control over Financial Reporting

We have audited AVEO Pharmaceuticals, Inc.'s internal control over financial reporting as of December 31, 2018, based on criteria established in Internal Control—Integrated Framework issued by the Committee of Sponsoring Organizations of the Treadway Commission (2013 framework) (the COSO criteria). In our opinion, AVEO Pharmaceuticals, Inc. (the Company) maintained, in all material respects, effective internal control over financial reporting as of December 31, 2018, based on the COSO criteria.

We also have audited, in accordance with the standards of the Public Company Accounting Oversight Board (United States) (PCAOB), the consolidated balance sheets of the Company as of December 31, 2018 and 2017, the related consolidated statements of operations, comprehensive loss, stockholders' deficit, and cash flows for each of the three years in the period ended December 31, 2018, and the related notes and our report dated March 14, 2019 expressed an unqualified opinion thereon that included an explanatory paragraph regarding the Company's ability to continue as a going concern.

Basis for Opinion

The Company's management is responsible for maintaining effective internal control over financial reporting and for its assessment of the effectiveness of internal control over financial reporting included in the accompanying Management's Report on Internal Control Over Financial Reporting. Our responsibility is to express an opinion on the Company's internal control over financial reporting based on our audit. We are a public accounting firm registered with the PCAOB and are required to be independent with respect to the Company in accordance with the U.S. federal securities laws and the applicable rules and regulations of the Securities and Exchange Commission and the PCAOB.

We conducted our audit in accordance with the standards of the PCAOB. Those standards require that we plan and perform the audit to obtain reasonable assurance about whether effective internal control over financial reporting was maintained in all material respects.

Our audit included obtaining an understanding of internal control over financial reporting, assessing the risk that a material weakness exists, testing and evaluating the design and operating effectiveness of internal control based on the assessed risk, and performing such other procedures as we considered necessary in the circumstances. We believe that our audit provides a reasonable basis for our opinion.

Definition and Limitations of Internal Control Over Financial Reporting

A company's internal control over financial reporting is a process designed to provide reasonable assurance regarding the reliability of financial reporting and the preparation of financial statements for external purposes in accordance with generally accepted accounting principles. A company's internal control over financial reporting includes those policies and procedures that (1) pertain to the maintenance of records that, in reasonable detail, accurately and fairly reflect the transactions and dispositions of the assets of the company; (2) provide reasonable assurance that transactions are recorded as necessary to permit preparation of financial statements in accordance with generally accepted accounting principles, and that receipts and expenditures of the company are being made only in accordance with authorizations of management and directors of the company; and (3) provide reasonable assurance regarding prevention or timely detection of unauthorized acquisition, use, or disposition of the company's assets that could have a material effect on the financial statements.

Because of its inherent limitations, internal control over financial reporting may not prevent or detect misstatements. Also, projections of any evaluation of effectiveness to future periods are subject to the risk that controls may become inadequate because of changes in conditions, or that the degree of compliance with the policies or procedures may deteriorate.

/s/ Ernst & Young LLP

Boston, Massachusetts
March 14, 2019

Changes in Internal Control Over Financial Reporting

There have been no changes in our internal control over financial reporting, as such term is defined in Rules 13a-15(f) and 15(d)-15(f) promulgated under the Securities Exchange Act of 1934, during the fourth quarter of 2018 that have materially affected, or is reasonably likely to materially affect, our internal control over financial reporting.

ITEM 9B. Other Information

None.

PART III

ITEM 10. Directors, Executive Officers and Corporate Governance

The information required by this Item 10 will be contained in the sections entitled "Election of Directors," "Corporate Governance" and "Section 16(a) Beneficial Ownership Reporting Compliance" appearing in the definitive proxy statement we will file in connection with our 2019 Annual Meeting of Stockholders and is incorporated by reference herein. The information required by this item relating to executive officers may be found in Part I, Item 1 of this Annual Report on Form 10-K under the heading "Business—Executive Officers of the Registrant" and is incorporated herein by reference.

ITEM 11. Executive Compensation

The information required by this Item 11 will be contained in the sections entitled "Executive and Director Compensation," "Executive and Director Compensation—Compensation Committee Interlocks and Insider Participation" and "Executive and Director Compensation—Compensation Committee Report" appearing in the definitive proxy statement we will file in connection with our 2019 Annual Meeting of Stockholders and is incorporated by reference herein.

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

The information required by this Item 12 will be contained in the sections entitled "Ownership of Our Common Stock" and "Executive and Director Compensation—Equity Compensation Plan Information" appearing in the definitive proxy statement we will file in connection with our 2019 Annual Meeting of Stockholders and is incorporated by reference herein.

ITEM 13. Certain Relationships and Related Person Transactions, and Director Independence

The information required by this Item 13 will be contained in the sections entitled "Certain Relationships and Related Person Transactions" appearing in the definitive proxy statement we will file in connection with our 2019 Annual Meeting of Stockholders and is incorporated by reference herein.

ITEM 14. Principal Accounting Fees and Services

The information required by this Item 14 will be contained in the section entitled "Corporate Governance—Principal Accountant Fees and Services" appearing in the definitive proxy statement we will file in connection with our 2019 Annual Meeting of Stockholders and is incorporated by reference herein.

PART IV

ITEM 15. Exhibits, Financial Statement Schedules

(a) Documents filed as part of Form 10-K.

(1) Financial Statements

Report of Independent Registered Public Accounting Firm

Consolidated Balance Sheets

Consolidated Statements of Operations

Consolidated Statements of Comprehensive Loss) Income

Consolidated Statements of Stockholders' (Deficit) Equity

Consolidated Statements of Cash Flows

Notes to Consolidated Financial Statements

(2) Schedules

Schedules have been omitted as all required information has been disclosed in the financial statements and related footnotes.

(3) Exhibits

The Exhibits listed in the Exhibit Index are filed as a part of this Form 10-K.

ITEM 16. Form 10-K Summary

None.

EXHIBIT INDEX

Exhibit Number	Description of Exhibit	Incorporated by Reference				Filed Herewith
		Form	File Number	Date of Filing	Exhibit Number	
	Articles of Incorporation and Bylaws					
3.1	Restated Certificate of Incorporation of the Registrant	8-K	001-34655	03/18/2010	3.1	
3.2	Certificate of Amendment of Restated Certificate of Incorporation of the Registrant	8-K	001-34655	06/03/2015	3.1	
3.3	Certificate of Amendment of Restated Certificate of Incorporation of the Registrant	10-Q	001-34655	08/09/2017	3.1	
3.4	Second Amended and Restated Bylaws of the Registrant	S-1/A	333-163778	02/08/2010	3.5	
	Instruments Defining the Rights of Security Holders, Including Indentures					
4.1	Specimen Stock Certificate evidencing the shares of common stock	S-1/A	333-163778	03/09/2010	4.1	
4.2	Registration Rights Agreement, dated May 13, 2016, by and among the Company and the Investors named therein	8-K	001-34655	05/13/2016	10.3	
4.3	Warrant Agreement, dated July 16, 2018, by and among the Company and Computershare Inc. and Computershare Trust Company, N.A., acting jointly as Warrant Agent	8-K	001-34655	07/16/2018	4.1	
	Material Contracts—Management Contracts and Compensatory Plans					
10.1	2002 Stock Incentive Plan, as amended	S-1/A	333-163778	02/23/2010	10.1	
10.2	Form of Incentive Stock Option Agreement under 2002 Stock Incentive Plan	S-1	333-163778	12/16/2009	10.2	
10.3	Form of Nonstatutory Stock Option Agreement under 2002 Stock Incentive Plan	S-1	333-163778	12/16/2009	10.3	
10.4	Form of Restricted Stock Agreement under 2002 Stock Incentive Plan	S-1	333-163778	12/16/2009	10.4	
10.5	Second Amended and Restated 2010 Stock Incentive Plan	8-K	001-34655	06/27/2017	99.1	
10.6	Form of Incentive Stock Option Agreement under 2010 Stock Incentive Plan	S-1/A	333-163778	02/08/2010	10.6	
10.7	Form of Nonqualified Stock Option Agreement under 2010 Stock Incentive Plan	S-1/A	333-163778	02/08/2010	10.7	
10.8	Form of Restricted Stock Agreement under 2010 Stock Incentive Plan	10-K	001-34655	03/30/2012	10.8	
10.9	Key Employee Change in Control Severance Benefits Plan	S-1	333-163778	12/16/2009	10.8	
10.10	2010 Employee Stock Purchase Plan, as amended	S-1/A	333-163778	02/23/2010	10.17	
10.11	Amendment No. 1 to 2010 Employee Stock Purchase Plan	8-K	001-34655	06/04/2013	99.2	
10.12	Offer Letter by Registrant to Michael Bailey, dated as of January 6, 2015	10-Q	001-34655	05/07/2015	10.1	
10.13	Severance Agreement, dated September 13, 2010, by and between the Registrant and Michael Bailey	10-Q	001-34655	11/05/2010	10.1	
10.14	Letter Agreement regarding Retention Bonus Award and Severance Agreement, dated February 3, 2014, by and between the Company and Michael Bailey	10-K	001-34655	3/13/2014	10.22	
10.15	Offer Letter by the Registrant to Michael Needle, dated January 8, 2015	10-Q	001-34655	05/07/2015	10.4	

Exhibit Number	Description of Exhibit	Incorporated by Reference				Filed Herewith
		Form	File Number	Date of Filing	Exhibit Number	
10.16	Severance and Change in Control Agreement, dated as of January 9, 2015, by and between the Registrant and Michael Needle	10-Q	001-34655	05/07/2015	10.2	
10.17	Offer Letter by and between the Registrant and Matthew Dallas, dated May 8, 2017	8-K	001-34655	05/17/2017	10.1	
10.18	Severance and Change in Control Agreement, dated November 20, 2017, by and between the Registrant and Matthew Dallas	8-K	001-34655	11/20/2017	10.1	
10.19	Offer Letter by and between the Registrant and Nikhil Mehta, dated November 10, 2017	10-K	001-34655	3/13/2018	10.21	
10.20	Severance and Change in Control Agreement, dated November 20, 2017, by and between the Registrant and Nikhil Mehta	10-K	001-34655	3/13/2018	10.22	
10.21	Offer Letter by and between the Registrant and Karuna Rubin dated June 16, 2015					X
10.22	Severance and Change in Control Agreement, dated March 13, 2019, by and between the Registrant and Karuna Rubin					X
	Material Contracts—Financing Agreements					
10.23	Securities Purchase Agreement, dated May 13, 2016, by and among the Company and the Investors named therein	8-K	001-34655	05/13/2016	10.1	
10.24	Form of Warrant to Purchase Common Stock	8-K	001-34655	05/13/2016	10.2	
10.25	Amended and Restated Loan and Security Agreement, dated December 28, 2017, by and among the Registrant and the parties named therein.	8-K	001-34655	01/02/2018	10.1	
10.26	Sales Agreement dated February 16, 2018, by and between the Company and Leerink Partners LLC	8-K	001-34655	02/16/2018	1.1	
	Material Contracts—License and Strategic Partnership Agreements					
10.27†	License Agreement, dated as of December 21, 2006, by and between the Registrant and Kirin Brewery Co. Ltd.	S-1	333-163778	12/16/2009	10.22	
10.28†	Option and License Agreement, dated as of March 18, 2009, by and between the Registrant and Biogen Idec International GmbH	S-1	333-163778	12/16/2009	10.26	
10.29†	Amendment No. 1 to Option and License Agreement, dated as of March 18, 2014 by and between the Registrant and Biogen Idec MA Inc.	10-Q	001-34655	05/07/2014	10.1	
10.30†	Co-Development and Collaboration Agreement, dated as of April 9, 2014 by and between the Registrant and Biodesix Inc.	10-Q	001-34655	05/07/2014	10.2	
10.31†	License Agreement, dated August 13, 2015, by and between the Registrant and Novartis International Pharmaceutical Ltd.	10-Q	001-34655	11/09/2015	10.2	
10.32†	Amended and Restated License Agreement, dated August 13, 2015, by and between the Registrant and St. Vincent's Hospital Sydney Limited	10-Q	001-34655	11/09/2015	10.3	
10.33†	License Agreement, dated December 18, 2015, by and between the Registrant and EUSA Pharma (UK) Limited	10-K	001-34655	03/15/2016	10.42	

Exhibit Number	Description of Exhibit	Incorporated by Reference				Filed Herewith
		Form	File Number	Date of Filing	Exhibit Number	
10.34†	Collaboration and License Agreement, dated March 17, 2016, by and between the Registrant and CANbridge Life Sciences Ltd.	10-Q	001-34655	05/10/2016	10.1	
10.35†	First Amendment, dated October 14, 2016, to Co-Development and Collaboration Agreement, dated April 9, 2014, by and between the Company and Biodesix, Inc.	10-Q	001-34655	11/04/2016	10.1	
10.36††	Agreement, dated December 18, 2018, by and between the Registrant and Novartis International Pharmaceutical Ltd.					X
	Additional Exhibits					
10.37	Memorandum of Understanding, dated December 26, 2017, by and among the Company and the parties named therein	8-K	001-34655	12/26/2017	10.1	
10.38	Stipulation of Settlement, dated January 29, 2018, by and among the Company and the parties named therein	10-Q	001-34655	5/8/2018	10.2	
21.1	Subsidiaries of the Registrant					X
23.1	Consent of Ernst & Young LLP					X
31.1	Certification of principal executive officer pursuant to Rule 13a-14(a)/15d-14(a) of the Securities Exchange Act of 1934, as amended.					X
31.2	Certification of principal financial officer pursuant to Rule 13a-14(a)/15d-14(a) of the Securities Exchange Act of 1934, as amended.					X
32.1	Certification of principal executive officer pursuant to 18 U.S.C. §1350, as adopted pursuant to Section 906 of the Sarbanes-Oxley Act of 2002.					X
32.2	Certification of principal financial officer pursuant to 18 U.S.C. §1350, as adopted pursuant to Section 906 of the Sarbanes-Oxley Act of 2002.					X
101.INS	XBRL Instance Document.					X
101.SCH	XBRL Taxonomy Extension Schema Document.					X
101.CAL	XBRL Taxonomy Calculation Linkbase Document.					X
101DEF	XBRL Taxonomy Extension Definition Linkbase Document.					X
101.LAB	XBRL Taxonomy Label Linkbase Document.					X
101.PRE	XBRL Taxonomy Presentation Linkbase Document.					X

† Confidential treatment has been granted as to certain portions, which portions have been omitted and separately filed with the Securities and Exchange Commission.

†† Confidential treatment has been requested as to certain portions, which portions have been omitted and separately filed with the Securities and Exchange Commission.

SIGNATURES

Pursuant to the requirements of Section 13 or 15(d) of the Securities Exchange Act of 1934, the registrant has duly caused this report to be signed on its behalf by the undersigned, thereunto duly authorized.

AVEO PHARMACEUTICALS, INC.

Date: March 14, 2019

By: /s/ MICHAEL BAILEY
Michael Bailey
President & Chief Executive Officer
(Principal Executive Officer)

Pursuant to the requirements of the Securities Exchange Act of 1934, this report has been signed below by the following persons on behalf of the registrant and in the capacities and on the dates indicated.

Signature	Title	Date
/s/ Michael Bailey **Michael Bailey**	President, Chief Executive Officer and Director *Principal Executive Officer*	March 14, 2019
/s/ MATTHEW DALLAS **Matthew Dallas**	Chief Financial Officer *Principal Financial and Accounting Officer*	March 14, 2019
/s/ Kenneth M. Bate **Kenneth M. Bate**	Director	March 14, 2019
/s/ Anthony B. Evnin **Anthony B. Evnin**	Director	March 14, 2019
/s/ ROBERT C. YOUNG **Robert C. Young**	Director	March 14, 2019
/s/ GREGORY T. MAYES **Gregory T. Mayes**	Director	March 14, 2019

AVEO Pharmaceuticals, Inc.
1 Broadway, 14th Floor
Cambridge, MA 02142
p. 617.588.1960

EXHIBIT 10.21

June 16, 2015

Karuna Rubin
[address]
[address]

Dear Karuna:

It is with great pleasure that we extend you this offer of employment to join AVEO Pharmaceuticals. The following letter sets forth the proposed terms and conditions of your offer of employment.

Position. Your position will be **Senior Corporate Counsel** reporting to Michael Boretti, Vice President, Corporate Development & Alliance Management. As a full-time employee we expect that you will devote your full time energies to the business and affairs of AVEO. If you accept this offer, your employment with the Company shall commence on a mutually agreed upon date.

Compensation:

- **Base Salary.** Your initial annual salary will be $210,000 paid semi-monthly. You will be eligible for a salary review in our 2015 common review cycle, and any changes to your salary will be pro-rated based on your effective date of employment.

- **Incentive Bonus.** Commencing in 2016, you will be eligible to participate in AVEO's performance-based incentive bonus program. Your bonus target is 20% of your base annual salary and is subject to corporate and individual performance assessments. Payment of the annual bonus requires approval by the AVEO Board of Directors and is pro-rated based on your effective date of employment.

- **Incentive Stock Options.** Subject to approval of the Company's Option Committee, the Company shall grant you incentive stock options to purchase 35,000 shares of common stock pursuant to the Company's 2010 Equity Incentive Plan.

  AVEO grants the options offered to newly hired employees after start of employment, on the first Tuesday of every month and, accordingly, the purchase price for your options will be the closing price of the common stock per share on NASDAQ on such grant date. The new hire options will vest over 4 years from your hire date with 25% of the options vesting after 12 months and the remainder on a monthly basis thereafter.

  Commencing in 2016, you will be also eligible to participate in the Company's annual renewal equity program. Subject to the Company's Option Committee approval, your renewal incentive stock options will be based on your performance and pro-rated to your effective date of employment. The renewal options will vest on a monthly basis over 4 years from the grant date.

AVEO Pharmaceuticals, Inc.
1 Broadway, 14th Floor
Cambridge, MA 02142
p. 617.588.1960

Benefits. The Company offers a competitive benefits program. As an employee, you will be eligible to participate in the family health, dental, individual life, and disability insurance; a 401(k) savings plan; three weeks of paid vacation per year accrued on per pay period basis; twelve paid holidays a year; flexible spending accounts for eligible medical and dependent care expenses; and a commuter assistance program. For more details, please refer to the enclosed Benefits Summary.

Contingencies. Your offer of employment is contingent upon AVEO's review and determination of a successful completion of a background investigation, which may include an evaluation of both your credit and criminal history.

On your start date you will be required to sign a standard employee Invention and Non-Disclosure Agreement attached hereto as Exhibit A.

Further, the Federal government requires you to provide proper identification verifying your eligibility to work in the United States. Please bring documents necessary to complete the Employment Eligibility Verification Form I-9 on your first date of employment. Refer to the enclosed Form I-9 for a list of acceptable documents.

Miscellaneous. This offer of employment is intended to outline the terms of compensation and benefits available to you should you choose to accept this position. It is not intended to imply any contract or contractual rights. Your employment will be at-will. Accordingly, you or the Company may end the employment relationship for any reason, at any time.

This letter, together with the Invention and Non-Disclosure Agreement to be executed by you and the Company, constitutes our entire offer regarding the terms and conditions of your prospective employment by the Company. It supersedes any prior agreements, or other promises or statements (whether oral or written) regarding the offered terms of employment.

If you decide to accept the terms of this letter, please sign one of the enclosed copies and return it to our office (attn: Human Resources.) This offer of employment is valid until June 23, 2015.

Karuna, we are very excited about having you join AVEO and have every expectation of a productive and rewarding relationship together. If you have any questions regarding this offer, please call Tracey Janesheski at 617-949-6845.

AVEO PHARMACEUTICALS, INC.

By: /s/ Michael Bailey
Michael Bailey
President & CEO

Accepted and Agreed:

By: /s/ Karuna Rubin

EXHIBIT 10.22

SEVERANCE AND CHANGE IN CONTROL AGREEMENT

THIS SEVERANCE AND CHANGE IN CONTROL AGREEMENT (the "Agreement"), made this 13th day of March 2019 (the "Effective Date"), is entered into by AVEO Pharmaceuticals, Inc., a Delaware corporation with its principal place of business at 1 Broadway 14th Floor, Cambridge, MA 02142 (the "Company"), and Karuna Rubin (the "Employee").

WHEREAS, the Company has determined that appropriate steps should be taken to reinforce and encourage the employment and dedication of the Employee and the Employee's efforts to maximize the Company's value.

NOW, THEREFORE, as an inducement for and in consideration of the Employee's employment with the Company and as consideration for the Employee's agreement to enter into and be bound by the provisions of Section 4 hereof, the Company agrees that the Employee shall receive the severance benefits set forth in this Agreement in the event the Employee's employment with the Company is terminated under the circumstances described below.

1. Key Definitions.

As used herein, the following terms shall have the following respective meanings:

1.1 "Cause" means conduct involving one or more of the following: (i) the conviction of the Employee of, or, plea of guilty or nolo contendere to, any crime involving dishonesty or any felony; (ii) the willful misconduct by the Employee resulting in material harm to the Company; (iii) fraud, embezzlement, theft or dishonesty by the Employee against the Company resulting in material harm to the Company; (iv) the repeated and continuing failure of the Employee to follow the proper and lawful directions of the Company's Chief Executive Officer or the Board after a written demand is delivered to the Employee that specifically identifies the manner in which the Chief Executive Officer or the Board believes that the Employee has failed to follow such instructions; (v) the Employee's current alcohol or prescription drug abuse affecting work performance, or current illegal use of drugs regardless of the effect on work performance; (vi) material violation of the Company's code of conduct by the Employee that causes harm to the Company; or (vii) the Employee's material breach of any term of the Agreement, or any other applicable confidentiality and/or non-competition agreements with the Company.

1.2 "Good Reason" means the occurrence, without the Employee's written consent, of any of the following events: (A) any material diminution in the Employee's duties, responsibilities or authority, or (B) a material reduction in the Employee's base salary (unless such reduction is effected in connection with a general and proportionate reduction of compensation for all employees of his or her level), provided, however, that Good Reason can only occur if (i) the Employee has given the Company a written notice of termination indicating the existence of a condition giving rise to Good Reason and the Company has not cured the condition giving rise to Good Reason within thirty (30) days after receipt of such notice of termination, and (ii) such notice of termination is given within ninety (90) days after the initial occurrence of the condition giving rise to Good Reason and further provided that a termination for Good Reason shall occur no more than one hundred eighty (180) days after the initial occurrence of the condition giving rise to Good Reason.

1.3 "Disability" means (i) the Employee is unable to engage in any substantial gainful activity by reason of any medically determinable physical or mental impairment that can be expected to result in death or can be expected to last for a continuous period of not less than twelve (12) months or (ii) the Employee is, by reason of any medically determinable physical or mental impairment that can be expected to result in death or can be expected to last for a continuous period of not less than twelve

(12) months, receiving income replacement benefits for a period of not less than three (3) months under an accident and health plan covering employees of the Company; provided that in each case, the Employee's physical or mental impairment shall be determined by an independent qualified physician mutually acceptable to the Company and the Employee (or her personal representative) or, if the Company and the Employee (or such representative) are unable to agree on an independent qualified physician, as determined by a panel of three physicians, one designated by the Company, one designated by the Employee (or her personal representative) and one designated by the two physicians so designated.

2. Termination Without Cause or for Good Reason.

2.1 Other than as set forth in Section 3 below, if the Employee's employment with the Company is terminated by the Company without Cause or due to the Employee's Disability, or by the Employee for Good Reason, then the Company shall:

(a) continue to pay the Employee her base salary in effect on the date of termination, to be paid in accordance with the Company's customary payroll practices as are established or modified from time to time for the period of time (the "Severance Period") until the earlier of (x) the date twelve (12) months following the date of termination, or (y) the date on which the Employee commences employment or a consulting relationship with substantially equivalent compensation;

(b) pay to the Employee (i) on the date of termination, any base salary earned but not paid and any vacation accrued but not used through the date of termination, and (ii) within thirty (30) days after the date of termination, any reimbursable business expenses incurred by the Employee through the date of termination pursuant to any expense reimbursement policies of the Company then in effect; and

(c) to the extent the Employee and any qualified beneficiary with respect to such Employee elects continuation of health benefit coverage under Section 4980B ("COBRA") of the Internal Revenue Code of 1986, as amended (the "Code"), and continues to be eligible for such benefits, the Company shall provide payments to the Employee for such benefits equal to the amount contributed for active employees with similar benefits and similar participating beneficiaries until the earlier of (x) the Severance Period, or (y) the date the Employee becomes eligible for group health coverage through another employer.

2.2 Except for the payments under Section 2(b) (which are not contingent upon the Employee's execution of a release of claims), the payments and benefits to the Employee under this Section 2 shall (i) be contingent upon the execution and non-revocation by the Employee of a general release of claims in favor of the Company, in the form provided by the Company at the time of the Employee's termination (the "Release") within sixty (60) days following the date of termination (the "Release Period"); provided that if the Release does not become effective during the Release Period, the payments and benefits described in Sections 2.1(a) and 2.1(c) of this Agreement that commenced following the date of termination shall cease following the Release Period and (ii) constitute the sole remedy of the Employee in the event of a termination of the Employee's employment in the circumstances set forth in this Section 2.

2.3 Notwithstanding anything herein to the contrary, all benefits under this Section 2 shall terminate immediately if the Employee, at any time, violates any proprietary information, assignment of inventions agreement, confidentiality, non-competition or non-solicitation obligation to the Company, or any other continuing obligation to the Company.

3. Termination upon a Change in Control.

If the Employee is an "Eligible Employee" as defined in the Key Employee Change in Control Benefits Plan adopted by the Company in December 2007, as amended and as may be amended in the

future (the current terms of which are attached hereto as Exhibit A) (the "Change in Control Plan") at the time of a Change in Control, as defined in said Change in Control Plan, then any termination of the Employee's employment following such Change in Control shall be governed by the terms of the Change in Control Plan and no benefits shall be provided under the terms of this Agreement.

4. Non-Competition and Non-Solicitation.

4.1 Restricted Activities. While the Employee is employed by the Company and for a period of one (1) year after the termination or cessation of such employment for any reason, the Employee will not:

(a) directly engage in the development or commercialization of a Competitive Product for another business or enterprise. For purposes of this provision, a "Competitive Product" means any therapeutic or diagnostic product that competes with any product that the Company (i) has, as of the date of cessation of the Employee's employment with the Company, developed to the stage of readiness for a phase 2 clinical trial or later; or (ii) has sold at any time during the Employee's employment with the Company or plans to commence selling during the one year period after the cessation of the Employee's employment;

(b) directly or indirectly either alone or in association with others (i) solicit, or permit any organization directly or indirectly controlled by the Employee to solicit, any employee of the Company to leave the employ of the Company, or (ii) solicit for employment, hire as an employee or engage as an independent contractor, or permit any organization directly or indirectly controlled by the Employee to solicit for employment, hire as an employee or engage as an independent contractor, any person who was employed or engaged by the Company at the time of the termination or cessation of the Employee's employment with the Company or within six months preceding such termination or cessation; provided, that this clause (ii) shall not apply to the solicitation, hiring or engagement of any individual whose employment with the Company has been terminated for a period of six months or longer; or

(c) directly or indirectly make any statements that are professionally or personally disparaging about, or adverse to, the interests of the Company (including its officers, directors, employees and consultants) including, but not limited to, any statements that disparage any person, product, service, finances, financial condition, capability or any other aspect of the Company's business, or engage in any conduct which could reasonably be expected to harm professionally or personally the Company's business or reputation (including its officers, directors, employees and consultants); provided that these obligations in Section 4.1(c) will not prevent the Employee from engaging in ordinary business competition with the Company after the provisions of Section 4.1(a) have expired, providing truthful information to any regulatory agency or providing truthful testimony in any litigation involving the Company or its officers, directors, employees and consultants.

If the Employee violates or breaches any of the provisions of this Section 4.1, then the provisions of this Section 4 shall be applicable to the Employee until a period of one year has expired without any violation or breach of such provisions.

4.2 Interpretation. If any restriction set forth in Section 4.1 is found by any court of competent jurisdiction to be unenforceable because it extends for too long a period of time or over too great a range of activities or in too broad a geographic area, it shall be interpreted to extend only over the maximum period of time, range of activities or geographic area as to which it may be enforceable.

4.3 Equitable Remedies. The restrictions contained in this Section 4 are necessary for the protection of the business and goodwill of the Company and are considered by the Employee to be reasonable for such purpose. The Employee agrees that any breach of this Section 4 is likely to cause the Company substantial and irrevocable damage which is difficult to measure. Therefore, in the event of any such breach or threatened breach, the Employee agrees that the Company, in addition to such other remedies

which may be available, shall have the right to obtain an injunction from a court restraining such a breach or threatened breach and the right to specific performance of the provisions of this Section 4 and the Employee hereby waives the adequacy of a remedy at law as a defense to such relief.

5. Taxes.

5.1 The payments set forth in Sections 2 and 3 above shall be subject to the withholding of such amounts, if any, relating to tax and other payroll deductions as the Company determines are reasonably required pursuant to any applicable law or regulation. Neither the Employee nor the Company shall have the right to accelerate or to defer the delivery of the payments to be made under Sections 2 and 3 of this Agreement.

5.2 Subject to this Section 5.2, payments or benefits under this Agreement shall begin only upon the date of a "separation from service" of the Employee (determined as set forth below) which occurs on or after the termination of the Employee's employment. The following rules shall apply with respect to distribution of the payments and benefits, if any, to be provided to the Employee under this Agreement:

(a) It is intended that each installment of the payments and benefits provided under this Agreement shall be treated as a separate "payment" for purposes of Section 409A of the Code and the guidance issued thereunder ("Section 409A"). Neither the Company nor the Employee shall have the right to accelerate or defer the delivery of any such payments or benefits except to the extent specifically permitted or required by Section 409A;

(b) If, as of the date of the "separation from service" of the Employee from the Company, the Employee is not a "specified employee" (each within the meaning of Section 409A), then each installment of the payments and benefits shall be made on the dates and terms set forth in this Agreement;

(c) If, as of the date of the "separation from service" of the Employee from the Company, the Employee is a "specified employee" (each, for purposes of this Agreement, within the meaning of Section 409A), then:

(x) Each installment of the payments and benefits due under this Agreement that, in accordance with the dates and terms set forth herein, will in all circumstances, regardless of when the separation from service occurs, be paid within the short-term deferral period (as defined in Section 409A) shall be treated as a short-term deferral within the meaning of Treasury Regulation Section 1.409A-1(b)(4) to the maximum extent permissible under Section 409A; and

(y) Each installment of the payments and benefits due under this Agreement that is not described in Section 5(c)(x) and that would, absent this subsection, be paid within the six-month period following the "separation from service" of the Employee of the Company shall not be paid until the date that is six months and one day after such separation from service (or, if earlier, the death of the Employee), with any such installments that are required to be delayed being accumulated during the six-month period and paid in a lump sum on the date that is six months and one day following the Employee's separation from service and any subsequent installments, if any, being paid in accordance with the dates and terms set forth herein; provided, however, that the preceding provisions of this sentence shall not apply to any installment of payments and benefits if and to the maximum extent that that such installment is deemed to be paid under a separation pay plan that does not provide for a deferral of compensation by reason of the application of Treasury Regulation 1.409A-1(b)(9)(iii) (relating to separation pay upon an involuntary separation from service). Such payments shall bear interest at an annual rate equal to the prime rate as set forth in the Eastern edition of the Wall Street Journal on the Date of Termination, from the Date of Termination to the date of payment. Any installments that qualify for the exception under Treasury Regulation

Section 1.409A-1(b)(9)(iii) must be paid no later than the last day of the second taxable year of the Employee following the taxable year of the Employee in which the separation from service occurs.

(d) The determination of whether and when a separation from service of the Employee from the Company has occurred shall be made and in a manner consistent with, and based on the presumptions set forth in, Treasury Regulation Section 1.409A-1(h). Solely for purposes of this Section 5(d), "Company" shall include all persons with whom the Company would be considered a single employer as determined under Treasury Regulation Section 1.409A-1(h)(3).

(e) All reimbursements and in-kind benefits provided under this Agreement shall be made or provided in accordance with the requirements of Section 409A to the extent that such reimbursements or in-kind benefits are subject to Section 409A, including, where applicable, the requirements that (i) any reimbursement is for expenses incurred during the Executive's lifetime (or during a shorter period of time specified in this Agreement), (ii) the amount of expenses eligible for reimbursement during a calendar year may not affect the expenses eligible for reimbursement in any other calendar year, (iii) the reimbursement of an eligible expense will be made on or before the last day of the calendar year following the year in which the expense is incurred and (iv) the right to reimbursement is not subject to set off or liquidation or exchange for any other benefit.

(f) Notwithstanding anything herein to the contrary, the Company shall have no liability to the Employee or to any other person if the payments and benefits provided in this Agreement that are intended to be exempt from or compliant with Section 409A are not so exempt or compliant.

6. Other Employment Termination. If the Employee's employment terminates for any reason other than as described in Sections 2 and 3, the Employee shall only receive any compensation owed to such Employee as of the termination date and any other post-termination benefits which the Employee is eligible to receive under any plan or program of the Company.

7. Successors.

7.1 Successor to Company. The Company shall require any successor (whether direct or indirect, by purchase, merger, consolidation or otherwise) to all or substantially all of the business or assets of the Company expressly to assume and agree to perform this Agreement to the same extent that the Company would be required to perform it if no such succession had taken place. All covenants and agreements hereunder shall inure to the benefit of and be enforceable by such successors or assigns without the necessity that this Agreement be re-signed at the time of such assignment. As used in this Agreement, "Company" shall mean the Company as defined above and any successor to its business or assets as aforesaid which assumes and agrees to perform this Agreement, by operation of law or otherwise.

7.2 Successor to Employee. This Agreement shall inure to the benefit of and be enforceable by the Employee's personal or legal representatives, executors, administrators, successors, heirs, distributees, devisees and legatees. If the Employee should die while any amount would still be payable to the Employee or the Employee's family hereunder if the Employee had continued to live, all such amounts, unless otherwise provided herein, shall be paid in accordance with the terms of this Agreement to the executors, personal representatives or administrators of the Employee's estate.

8. Notices. All notices, instructions and other communications given hereunder or in connection herewith shall be in writing. Any such notice, instruction or communication shall be sent either (i) by registered or certified mail, return receipt requested, postage prepaid, or (ii) prepaid via a reputable nationwide overnight courier service, in each case addressed to the Company, at 1 Broadway 14th Floor, Cambridge, MA 02142, ATTN: Michael Bailey, Chief Executive Officer, and to the Employee at the Employee's address indicated in the introduction to this Agreement (or to such other address as either the Company or the Employee may have furnished to the other in writing in accordance herewith). Any such notice, instruction or communication shall be deemed to have been delivered five business days after it is sent by registered or certified mail, return receipt requested, postage prepaid, or one business day after it

is sent via a reputable nationwide overnight courier service. Either party may give any notice, instruction or other communication hereunder using any other means, but no such notice, instruction or other communication shall be deemed to have been duly delivered unless and until it actually is received by the party for whom it is intended.

9. Miscellaneous.

9.1 Employment by Subsidiary. For purposes of this Agreement, the Employee's employment with the Company shall not be deemed to have terminated solely as a result of the Employee continuing to be employed by a wholly-owned subsidiary of the Company.

9.2 Severability. The invalidity or unenforceability of any provision of this Agreement shall not affect the validity or enforceability of any other provision of this Agreement, which shall remain in full force and effect.

9.3 Governing Law. The validity, interpretation, construction and performance of this Agreement shall be governed by the internal laws of the Commonwealth of Massachusetts, without regard to conflicts of law principles. The Employee hereby irrevocably submits to and acknowledges and recognizes the jurisdiction of the courts of the Commonwealth of Massachusetts, or if appropriate, a federal court located in Massachusetts (which courts, for purposes of this Agreement, are the only courts of competent jurisdiction), over any suit, action or other proceeding arising out of, under or in connection with this Agreement or the subject matter hereof.

9.4 Waiver of Right to Jury Trial. Both the Company and the Employee expressly waive any right that any party either has or may have to a jury trial of any dispute arising out of or in any way related to the matters covered by this Agreement.

9.5 Waivers. No waiver by the Employee at any time of any breach of, or compliance with, any provision of this Agreement to be performed by the Company shall be deemed a waiver of that or any other provision at any subsequent time.

9.6 Counterparts. This Agreement may be executed in counterparts, each of which shall be deemed to be an original but both of which together shall constitute one and the same instrument.

9.7 Entire Agreement. Except to the extent provided herein, this Agreement, together with the offer letter and the Invention and Non-Disclosure Agreement, each to be executed by you and the Company, sets forth the entire agreement of the parties hereto in respect of the subject matter contained herein and supersedes all prior agreements, promises, covenants, arrangements, communications, representations or warranties, whether oral or written, by any officer, employee or representative of any party hereto in respect of the subject matter contained herein.

9.8 Not an Employment Contract. The Employee acknowledges that this Agreement does not constitute a contract of employment or impose on the Company any obligation to retain the Employee as an employee and that this Agreement does not prevent the Employee from terminating employment at any time.

9.9 Amendments. This Agreement may be amended or modified only by a written instrument executed by both the Company and the Employee, and, notwithstanding the provisions of the Change in Control Plan, the language of such Change in Control Plan may not be amended as it applies to the Employee except to the extent subject to a written instrument executed by both parties.

9.10 Employee's Acknowledgements. The Employee acknowledges that she: (a) has read this Agreement; (b) has been represented in the preparation, negotiation and execution of this Agreement by

legal counsel of the Employee's own choice or has voluntarily declined to seek such counsel; and (c) understands the terms and consequences of this Agreement.

9.11 Representations Regarding Prior Work. You represent that you have no agreement or other legal obligation with any prior employer or any other person or entity that restricts your ability to engage in employment discussion with, employment with or to perform function for, the Company. You represent that you have been advised by the Company that at no time should you divulge to or use for the benefit of the Company, any trade secret or proprietary information of any previous employer. You acknowledge that you have not divulged or used any such information for the benefit of the Company. You acknowledge that the Company is basing important business decision on these representations, affirm that all of the statements included herein are true and that any breach of this Section 9.11 would be considered a material breach of this Agreement.

[Remainder of page intentionally left blank]

IN WITNESS WHEREOF, the parties hereto have executed this Agreement as of the day and year set forth above.

AVEO Pharmaceuticals, Inc.

By: /s/ Michael Bailey

Title: President & CEO

Karuna Rubin

/s/ Karuna Rubin

EXHIBIT A

AVEO PHARMACEUTICALS, INC.

KEY EMPLOYEE CHANGE IN CONTROL BENEFITS PLAN

SECTION 1. INTRODUCTION

The Key Employee Change in Control Benefits Plan (the "Plan") is designed to provide separation pay and benefits to certain eligible employees of AVEO Pharmaceuticals, Inc. ("the "Company") whose employment is involuntarily terminated without cause or voluntarily terminated for good reason as set forth in this Plan.

SECTION 2. DEFINITIONS

For purposes of this Plan, the following terms shall have the meanings set forth below:

(a) "BASE SALARY" means the annual base salary for an Eligible Employee as in effect on the Change in Control Date, or as increased thereafter.

(b) "BOARD" means the Board of Directors of the Company.

(c) "CAUSE" means conduct involving one or more of the following: (i) the conviction of the Eligible Employee of, or, plea of guilty or nolo contendere to, any crime involving dishonesty or any felony; (ii) the willful misconduct by the Eligible Employee resulting in material harm to the Company; (iii) fraud, embezzlement, theft or dishonesty by the Eligible Employee against the Company resulting in material harm to the Company; (iv) the repeated and continuing failure of the Eligible Employee to follow the proper and lawful directions of the Company's Chief Executive Officer or the Board after a written demand is delivered to the Eligible Employee that specifically identifies the manner in which the Chief Executive Officer or the Board believes that the Employee has failed to follow such instructions; (v) the Eligible Employee's current alcohol or prescription drug abuse affecting work performance, or current illegal use of drugs regardless of the effect on work performance; (vi) material violation of the Company's code of conduct by the Eligible Employee that causes harm to the Company; or (vii) the Eligible Employee's material breach of any term of the Plan or any applicable written proprietary information, confidentiality, non-competition and/or non-solicitation agreements with the Company.

(d) "CHANGE IN CONTROL" means the occurrence of any of the events set forth in subsections (A) or (B) below, provided that such event(s) constitute (i) a change in the ownership of the Company (as defined in Treasury Regulation Section 1.409A-3(i)(5)(v)), (ii) a change in effective control of the Company (as defined in Treasury Regulation Section 1.409A-3(i)(5)(vi)), or (iii) a change in the ownership of a substantial portion of the assets of the Company (as defined in Treasury Regulation Section 1.409A-3(i)(5)(vii)):

(A) when a person, entity or group (within the meaning of Section 13(d)(3) or 14(d)(2) of the Securities Exchange Act of 1934, a amended) acquires beneficial ownership of the Company's capital stock equal to 50% or more of either: (X) the then-outstanding shares of the Company's common stock (the "Outstanding Company Common Stock") or (Y) the combined voting power of the Company's then-outstanding securities entitled to vote generally in the election of directors (the "Outstanding Company Voting Securities") provided, however, that for purposes of this subsection (A), the following acquisitions of securities shall not constitute a Change in Control: (1) any acquisition of securities directly from the Company (excluding an acquisition of securities pursuant to the exercise, conversion or exchange of any security exercisable for, convertible into or exchangeable for common stock or voting securities of the Company, unless the Person exercising,

converting or exchanging such security acquired such security directly from the Company or an underwriter or agent of the Company) or (2) any acquisition of securities by the Company; or

(B) upon the consummation by the Company of a reorganization, merger, consolidation, statutory share exchange or a sale or other disposition of all or substantially all of the assets of the Company in one or a series of transactions (a "Business Combination"), provided that, in each case, the persons who were the Company's beneficial owners of the Outstanding Company Common Stock and Outstanding Company Voting Securities immediately prior to such Business Combination do not beneficially own, directly or indirectly, more than 50% of the then-outstanding shares of common stock and the combined voting power of the then-outstanding securities entitled to vote generally in the election of directors, respectively, of the resulting or acquiring corporation in such Business Combination (which shall include, without limitation, a corporation which as a result of such transaction owns the Company or substantially all of the Company's assets either directly or through one or more subsidiaries) in substantially the same proportions as their ownership, immediately prior to such Business Combination, of the Outstanding Company Common Stock and Outstanding Company Voting Securities, respectively; or

(C) such time as the Continuing Directors (as defined below) do not constitute a majority of the Board (or, if applicable, the Board of Directors of a successor corporation to the Company), where the term "Continuing Director" means at any date a member of the Board (i) who was a member of the Board on the effective date of this Plan, or (ii) who was nominated or elected subsequent to such date by at least a majority of the directors who were Continuing Directors at the time of such nomination or election or whose election to the Board was recommended or endorsed by at least a majority of the directors who were Continuing Directors at the time of such nomination or election; provided, however, that there shall be excluded from this clause (ii) any individual whose initial assumption of office occurred as a result of an actual or threatened election contest with respect to the election or removal of directors or other actual or threatened solicitation of proxies or consents, by or on behalf of a person other than the Board.

(e) "CHANGE IN CONTROL DATE" means the first date on which a Change in Control occurs.

(f) "DISABILITY" means (i) the Eligible Employee is unable to engage in any substantial gainful activity by reason of any medically determinable physical or mental impairment that can be expected to result in death or can be expected to last for a continuous period of not less than twelve (12) months or (ii) the Eligible Employee is, by reason of any medically determinable physical or mental impairment that can be expected to result in death or can be expected to last for a continuous period of not less than twelve (12) months, receiving income replacement benefits for a period of not less than three (3) months under an accident and health plan covering employees of the Company; provided that in each case, the Eligible Employee's physical or mental impairment shall be determined by an independent qualified physician mutually acceptable to the Company and the Eligible Employee (or his personal representative) or, if the Company and the Eligible Employee (or such representative) are unable to agree on an independent qualified physician, as determined by a panel of three physicians, one designated by the Company, one designated by the Eligible Employee (or his personal representative) and one designated by the two physicians so designated.

(g) "INVOLUNTARY TERMINATION WITHOUT CAUSE" means an Eligible Employee's dismissal or discharge by the Company (or, if applicable, by any successor entity) for a reason other than Cause. The termination of employment will not be deemed to be an "Involuntary Termination Without Cause" if such termination occurs as a result of the Eligible Employee's voluntary resignation without Good Reason, death or Disability.

(i) “MANAGEMENT TEAM” shall include any executive officer, senior vice-president and vice-president of the Company and other employees of the Company nominated by the Chief Executive Officer and ratified by the Compensation Committee.

(j) “QUALIFYING TERMINATION” means that an Eligible Employee’s employment terminates due to an Involuntary Termination Without Cause or a Voluntary Termination for Good Reason, in either case, within eighteen (18) months following a Change in Control Date.

(k) “SECTION 16 OFFICER” means an executive officer of the Company, other than the Chief Executive Officer, Chief Financial Officer, Chief Business Officer and Chief Medical Officer, who is considered to be an “officer” of the Company within the meaning of Rule 16a-1(f) under the Securities Exchange Act of 1934, as amended and “executive Officer” of the Company within the meaning of Rule 3b-7 under the Securities Exchange Act of 1934, as amended.

(l) “VOLUNTARY TERMINATION FOR GOOD REASON” means any action by the Company without the Eligible Employee’s prior consent which results in he or she voluntarily terminating his or her employment with the Company (or, if applicable, with any successor entity) after any of the following are undertaken by the Company (or, if applicable, by any successor entity) without such Eligible Employee’s express consent, provided, however, that a termination for Good Reason can only occur if (i) the Eligible Employee has given the Company a written notice of termination indicating the existence of a condition giving rise to Good Reason and the Company has not cured the condition giving rise to Good Reason within thirty (30) days after receipt of such notice of termination, and (ii) such notice of termination is given within ninety (90) days after the initial occurrence of the condition giving rise to Good Reason and further provided that a termination for Good Reason shall occur no more than one hundred eighty (180) days after the initial occurrence of the condition giving rise to Good Reason: (A) any requirement by the Company that the Eligible Employee perform his or her principal duties outside a radius of 50 miles from the Company’s Cambridge, Massachusetts location, (B) any material diminution in the Eligible duties, responsibilities or authority; or (C) a material reduction in the Eligible Employee’s base salary (unless such reduction is effected in connection with a general and proportionate reduction of compensation for all employees of his or her level).

SECTION 3. ELIGIBILITY AND PARTICIPATION

An individual is deemed an “Eligible Employee” and, therefore, eligible to participate in the Plan if he or she is a member of the Company’s Management Team at the time of such individual’s termination of employment with the Company, and such employment terminates due to an event which constitutes a Qualifying Termination.

SECTION 4. BENEFITS

Eligible Employees are eligible to receive the following benefits on the following conditions:

(a) SALARY AND BONUS PAYOUT. Commencing in the first month following the month of a Qualifying Termination and the Release set forth in Section (f) below becoming binding on the Eligible Employee, Eligible Employee will be paid in periodic installments consistent with the Company’s payroll procedures as then in effect and continuing for a number of months equal to the product of the Eligible Employee’s “Severance Multiple” (as set forth below) times twelve (12), a total sum equal to: (i) Severance Multiple times the Eligible Employee’s Base Salary; (ii) the Eligible Employee’s Severance Multiple times his/her target bonus on the date of the Qualifying Termination; and (iii) the Eligible Employee’s target bonus on the date of termination multiplied by a fraction, the numerator of which shall equal the number of days the Eligible Employee was employed by the Company during the Company fiscal year in which the termination occurs and the denominator of which shall equal 365.

Severance Multiple shall be based on the following:

Chief Executive Officer	—	1.5
Chief Financial Officer, Chief Business Officer, Chief Medical Officer, Section 16 Officer, and any other Eligible Employee nominated by the CEO and ratified by the Compensation Committee	—	1.0
Senior Vice Presidents, Vice Presidents and other Eligible Employees nominated by CEO and ratified by Compensation Committee, other than those considered Section 16 Officers	—	0.5

(b) HEALTH BENEFITS. Provided the Eligible Employee timely elects continued coverage under federal COBRA law, the Company shall pay, on the Eligible Employee's behalf, the portion of premiums for the type of group health insurance coverage, including coverage for his or her eligible dependents, that the Company paid prior to his or her termination of employment for a period following his or her Qualifying Termination based on the Eligible Employee's level as follows:

Chief Executive Officer	—	18 months
Chief Financial Officer, Chief Business Officer, Chief Medical Officer, Section 16 Officer, and any other Eligible Employee nominated by the CEO and ratified by the Compensation Committee	—	12 months
Senior Vice Presidents, Vice Presidents and other Eligible Employees nominated by CEO and ratified by Compensation Committee, other than those considered Section 16 Officers	—	6 months

provided, however, that the Company will pay such premiums for the Eligible Employee and his/her eligible dependents only for coverage for which such individual and those dependents were enrolled immediately prior to the Qualifying Termination. The Eligible Employee shall continue to be required to pay that portion of the premium of such group health insurance coverage, including coverage for his/her eligible dependents that he/she had been required to pay as an active employee immediately prior to the Qualifying Termination of employment (subject to change). For the balance of the period that an Eligible Employee is eligible to receive coverage under federal COBRA law, the Eligible Employee shall be eligible to maintain coverage for himself/herself and his/her eligible dependents at the Eligible Employee's own expense in accordance with applicable law.

(c) EQUITY ACCELERATION. In addition to any other rights that Eligible Employees may have with respect to the acceleration of the vesting of any stock options or restricted stock awards ("Awards") granted to such Eligible Employees pursuant to the Company's 2002 Stock Incentive Plan, as amended (the "2002 Stock Incentive Plan"), or any successor plan, including without limitation those certain change in control related acceleration rights (upon a termination without cause) approved by the Board on December 11, 2007, and notwithstanding any provision to the contrary contained in the 2002 Stock Incentive Plan, the instrument evidencing any Award or any other agreement between an Eligible Employee and the Company, each such Award shall be immediately exercisable in full and/or free of all restrictions on repurchase, as the case may be, if the Eligible Employee's employment with the Company or the acquiring or succeeding corporation is terminated as a result of a Qualifying Termination.

(d) EARNED BUT UNPAID BENEFITS. As of the Qualifying Termination date an Eligible Employee will also be eligible to receive any earned but unpaid benefits including salary earned but unpaid, the annual bonus for the most recently completed financial year and payment for unused accrued vacation.

(e) RELEASE. To receive benefits under this Plan, an Eligible Employee must execute a general release of claims in favor of the Company within thirty (30) days following the Eligible Employee's Qualifying Termination, in a form provided by the Company at the time of the Employee's Qualifying Termination, and such release must become effective in accordance with its terms (the "Release"). Notwithstanding the foregoing, if the 30th day following the Eligible Employee's Qualifying Termination occurs in the calendar year following the Eligible Employee's Qualifying Termination, then the payments and benefits will commence no earlier than January 1 of such subsequent calendar year.

(f) TERMINATION OF BENEFITS. Benefits under this Plan shall terminate immediately if an Eligible Employee, at any time, violates any proprietary information, confidentiality, non-competition or non-solicitation obligation to the Company, or any other continuing obligation to the Company.

(g) NON-DUPLICATION OF BENEFITS. Eligible Employees are not eligible to receive benefits under this Plan more than one time and are not eligible to receive benefits under any other Company change in control severance plan, arrangement or agreement.

(h) TAX WITHHOLDING. Any payments that an Eligible Employee receives under this Plan shall be subject to all required tax withholding.

(i) DISTRIBUTIONS. The following rules shall apply with respect to distribution of the payments and benefits, if any, to be provided to the Eligible Employee under this Section 4:

(A) It is intended that each installment of the payments and benefits provided under Section 4 shall be treated as a separate "payment" for purposes of Section 409A of the U.S. Internal Revenue Code of 1986, as amended, and the guidance issued thereunder ("Section 409A"). Neither the Company nor the Eligible Employee shall have the right to accelerate or defer the delivery of any such payments or benefits except to the extent specifically permitted or required by Section 409A;

(B) If, as of the date of the "separation from service" of the Eligible Employee from the Company, the Eligible Employee is not a "specified employee" (each within the meaning of Section 409A), then each installment of the payments and benefits shall be made on the dates and terms set forth in Section 4; and

(C) If, as of the date of the "separation from service" of the Eligible Employee from the Company, the Eligible Employee is a "specified employee" (each, for purposes of this Agreement, within the meaning of Section 409A), then:

(x) Each installment of the payments and benefits due under Section 4 that, in accordance with the dates and terms set forth herein, will in all circumstances, regardless of when the separation from service occurs, be paid within the Short-Term Deferral Period (as hereinafter defined) shall be treated as a short-term deferral within the meaning of Treasury Regulation Section 1.409A-1(b)(4) to the maximum extent permissible under Section 409A. For purposes of this Agreement, the "Short-Term Deferral Period" means the period ending on the later of the 15th day of the third month following the end of the Eligible Employee's tax year in which the Eligible Employee's separation from service occurs and the 15th day of the third month following the end of the Company's tax year in which the Eligible Employee's separation from service occurs; and

(y) Each installment of the payments and benefits due under Section 4 that is not paid within the Short-Term Deferral Period and that would, absent this subsection, be paid within the six-month period following the "separation from service" of the Eligible Employee of the Company shall not be paid until the date that is six months and one day after such separation from service (or, if earlier, the death of the Eligible Employee), with any such installments that are required to be delayed being accumulated during the six-month period and paid in a lump sum on the date that is six months and one day following the Eligible Employee's separation from service and any subsequent installments, if any, being paid in accordance with the dates and terms set forth herein; provided, however, that the preceding provisions of this sentence shall not apply to any installment of payments and benefits if and to the maximum extent that that such installment is deemed to be paid under a separation pay plan that does not provide for a deferral of compensation by reason of the application of Treasury Regulation 1.409A-1(b)(9)(iii) (relating to separation pay upon an involuntary separation from service) or Treasury Regulation 1.409A-1(b)(9)(v) (relating to reimbursements and certain other separation payments). Such payments shall bear interest at an annual rate equal to the prime rate as set forth in the Eastern edition of the Wall Street Journal on the Date of Termination, from the Date of Termination to the date of payment. Any installments that qualify for the exception under Treasury Regulation Section 1.409A-1(b)(9)(iii) must be paid no later than the last day of the second taxable year of the Eligible Employee following the taxable year of the Eligible Employee in which the separation from service occurs.

SECTION 5. OTHER TERMINATIONS

An otherwise Eligible Employee shall NOT be eligible to receive benefits under this Plan if (i) the Eligible Employee's employment terminates due to death, Disability or any other reason other than a Qualifying Termination; or (ii) an Eligible Employee's employment is terminated within thirty (30) days of his or her refusal to accept an offer of comparable employment by any successor to the Company (provided that "comparable employment" shall mean employment at a business office the location of which is not violative of Section 2(g)(i), with duties and responsibilities not violative of Section 2(g)(ii) and with a reduction in such Eligible Employee's base salary not violative of 2(g)(iii)).

SECTION 6. CLAIMS PROCEDURE

Ordinarily, severance benefits will be paid to an Eligible Employee without to having to file a claim or take any action other than signing the Release as provided in Section 4(f) of this Plan and, where applicable, not revoking the Release during the applicable revocation period. If an Eligible Employee believes that he or she is entitled to severance benefits under the Plan that are not being paid, he or she may submit a written claim for payment to the Company. Any claim for benefits shall be in writing, addressed to the Company and must be sufficient to notify the Company of the benefit claimed. If such claim is denied, the Company shall within a reasonable period of time provide a written notice of denial. The notice will include the specific reasons for denial, the provisions of the Plan on which the denial is based, and the procedure for a review of the denied claim. Where appropriate, it will also include a description of any additional material or information necessary to complete or perfect the claim and an explanation of why that material or information is necessary. Eligible Employees may request in writing a review of a claim denied by the Company and may review pertinent documents and submit issues and comments in writing to the Company. The Company shall provide a written decision upon such request for review of a denied claim. The decision of the Company upon such review shall be final.

SECTION 7. MISCELLANEOUS

The Company reserves the right to amend or terminate this Plan at any time; provided however, that this Plan may not be amended or terminated following the Change in Control Date; and further provided that Section 4(c) of this Plan shall not be amended without the Eligible Employee's consent unless the Board determines that the amendment, taking into account any other related action, would not materially adversely affect the Eligible Employee. This Plan shall be binding upon any surviving entity resulting from a Change in Control and upon any other person who is a successor by merger, acquisition, consolidation or otherwise to the business formerly carried on by the Company without regard to whether or not such person actively adopts or formally continues the Plan. The Plan shall be interpreted in accordance with the laws of the Commonwealth of Massachusetts. The Eligible Employee hereby irrevocably submits to and acknowledges and recognizes the jurisdiction of the courts of the Commonwealth of Massachusetts, or if appropriate, a federal court located in Massachusetts (which courts, for purposes of the Plan, are the only courts of competent jurisdiction), over any suit, action or other proceeding arising out of, under or in connection with the Plan or the subject matter hereof.

EXHIBIT 10.36

Confidential Materials omitted and filed separately with the
Securities and Exchange Commission. Double asterisks denote omissions.

AGREEMENT

Agreement (the "Agreement"), dated December 18, 2018 (the "Agreement Effective Date"), by and between Novartis International Pharmaceutical Ltd. ("Novartis") and AVEO Pharmaceuticals, Inc. ("AVEO"). Novartis and AVEO are separately referred to as a "Party" and are collectively referred to as the "Parties".

Background

Novartis and AVEO were parties to a License Agreement, dated August 13, 2015 (the "License Agreement") pursuant to which AVEO licensed to Novartis certain intellectual property rights Controlled by AVEO relating to a group of antibodies that bind to Growth Differentiation Factor 15 ("GDF15"), including an antibody referred to as AV-380 by AVEO (and NIK937 by Novartis) as well as the antibodies identified on Exhibit A to the License Agreement, together with any modified or derivative form of any such antibodies, including any fragment of, pegylated version of (whether or not including amino acid changes) and any other chemically modified versions (including associated amino acid substitutions) of such antibodies, and any fused or conjugated versions of any of the foregoing (the "Licensed Antibodies"). On June 28, 2018, Novartis sent a notice of termination of the License Agreement to AVEO, which became effective (pursuant to the License Agreement's terms) on August 27, 2018 (the "Date of Termination"). AVEO has indicated that it intends to continue development of the Licensed Antibodies, and the Parties are entering into this Agreement to memorialize certain understandings between the Parties with respect to the License Agreement and Novartis' support of the further development of the Licensed Antibodies by AVEO.

The Parties agree as follows:

Section 1. Definitions.

(a) Definitions. Unless the context otherwise requires, the terms in this Agreement with initial letters capitalized, will have the meanings set forth below, or the meaning as designated in the indicated places throughout this Agreement. Capitalized terms not otherwise defined herein have the same meaning as in the License Agreement.

"Accounting Standards" means, with respect to AVEO, US GAAP (United States Generally Accepted Accounting Principles and means, with respect to Novartis, IFRS (International Financial Reporting Standards), in each case as generally and consistently applied throughout the Party's organization. Each Party will promptly notify the other Party in the event that it changes the Accounting Standards pursuant to which its records relating to this Agreement are maintained; *provided, however*, that each Party may only use internationally recognized accounting principles (*e.g.*, IFRS, US GAAP, *etc.*).

"Affiliate" means, with respect to a Party, any Person that controls, is controlled by, or is under common control with that Party. For the purpose of this definition, "control" will mean, direct or indirect, ownership of 50% or more of the shares of stock entitled to vote for the election of directors, in the case of a corporation, or 50% or more of the equity interest in the case of any other type of legal entity, status as a general partner in any partnership, or any other arrangement whereby the entity or person controls or has the right to control the board of directors or equivalent governing body of a corporation or other entity, or the ability to cause the direction of the management or policies of a corporation or other entity, or otherwise has "control" over the relevant entity as set forth in applicable Accounting Standards, as amended from time to time. In the case of entities organized under the laws of certain countries, the maximum percentage ownership permitted by law for a foreign investor may be less than 50%, and in such case such lower percentage will be substituted in the preceding sentence if such foreign investor has the power to direct the management and policies of such entity.

"AVEO Indemnitees" has the meaning set forth in Section 6(b).

"BLA" means a Biologics License Application in the United States for authorization to market the Product, as defined in the applicable laws and regulations and filed with the FDA.

"Commercialize" means to market, promote, distribute, import, export, offer to sell and/or sell Product, and "Commercialization" means commercialization activities relating to Product, including activities relating to marketing, promoting, distributing, importing, exporting, offering for sale and/or selling the Licensed Antibodies.

"Control" or "Controlled" means, with respect to any Know-How, Patent Rights, other intellectual property rights, or any proprietary or trade secret information, the legal authority or right (whether by ownership, license or otherwise, other than by a license granted under this Agreement) of a Party or its Affiliates, to grant a license or a sublicense of or under such Know-How, Patent Rights, or intellectual property rights to another Person, or to otherwise disclose such proprietary or trade secret information to another Person, without breaching the terms of any agreement with a Third Party or misappropriating the proprietary or trade secret information of a Third Party.

"Claims" means all Third Party demands, claims, actions, proceedings and liability (whether criminal or civil, in contract, tort or otherwise) for losses, damages, reasonable legal costs and other reasonable expenses of any nature whatsoever.

"Develop" or "Development" means drug development activities, including, without limitation, test method development and stability testing, assay development and audit development, toxicology, formulation, quality assurance/quality control development, statistical analysis, clinical studies, packaging development, regulatory affairs, and the preparation, filing and prosecution of BLAs and MAAs.

"EMA" means the European Medicines Agency or any successor entity thereto.

"Exclusivity Product" has the meaning set forth in Section 5(a).

"FDA" means the United States Food and Drug Administration or any successor entity thereto.

"Field" means the treatment and prevention of diseases and other conditions in all indications in humans.

"ICC" has the meaning set forth in Section 9(e).

"Indemnification Claim Notice" has the meaning set forth in Section 6(c)(ii).

"Indemnified Party" has the meaning set forth in Section 6(c)(ii).

"Indemnifying Party" has the meaning set forth in Section 6(c)(ii).

"Information" means all Know-How and other proprietary information and data of a financial, commercial or technical nature which the disclosing Party, its Affiliates, or its or their licensors has supplied or otherwise made available to the other Party or its Affiliates, whether made available orally, in writing or in electronic form, including information comprising or relating to concepts, discoveries, inventions, data, designs or formulae in relation to this Agreement.

"Know-How" means all technical information, know-how and data, including inventions (whether patentable or not), discoveries, trade secrets, specifications, instructions, processes, formulae, materials, expertise and other technology applicable to compounds, formulations, compositions, products or to their manufacture, development, registration, use or commercialization or methods of assaying or testing them or processes for their manufacture, formulations containing them, compositions incorporating or comprising them and including all biological, chemical, pharmacological, biochemical, toxicological, pharmaceutical, physical and analytical, safety, quality control, manufacturing, preclinical and clinical data, instructions, processes, formulae, expertise and information, regulatory filings and copies thereof, relevant to the development, manufacture, use or commercialization of and/or which may be useful in studying, testing, development, production or formulation of products, or intermediates for the synthesis thereof.

"MAA" means an application for the authorization to market the Licensed Antibodies in any country or group of countries outside the United States, as defined in the applicable laws and regulations and filed with the Regulatory Authority of a given country or group of countries.

"Material" has the meaning set forth in Section 3.

"Novartis Indemnitees" has the meaning set forth in Section 6(a).

"Patent Rights" means all patents and patent applications, including all divisionals, continuations, substitutions, continuations-in-part, re-examinations, reissues, additions, renewals, extensions, registrations, supplemental protection certificates, utility models, design patents and the like of any of the foregoing.

"Person" means any individual, partnership, limited liability company, firm, corporation, association, trust, unincorporated organization or other entity.

"Product" means pharmaceutical products consisting of or incorporating one or more of the Licensed Antibodies.

"Regulatory Authority" means any governmental authority or agency responsible for authorizing or approving the marketing and/or sale of biologic products in a jurisdiction (*e.g.*, the FDA, EMA, the Japanese Ministry of Health, Labour and Welfare, and corresponding national or regional regulatory agencies or organizations).

"Third Party" means any Person other than a Party or an Affiliate of a Party.

(b) Interpretation. In this agreement unless otherwise specified

(i) "includes" and "including" will mean respectively includes and including without limitation

(ii) a Party includes its permitted assignees and/or the respective successors in title to substantially the whole of its undertaking;

(iii) a statute or statutory instrument or any of their provisions is to be construed as a reference to that statute or statutory instrument or such provision as the same may have been or may from time to time hereafter be amended or re-enacted

(iv) words denoting the singular will include the plural and vice versa and words denoting any gender will include all genders

(v) the Exhibits and other attachments form part of the operative provision of this Agreement and references to this Agreement shall, unless the context otherwise requires, include references to the Exhibits and attachments

(vi) the headings in this Agreement are for information only and will not be considered in the interpretation of this Agreement

(v) general words will not be given a restrictive interpretation by reason of their being preceded or followed by words indicating a particular class of acts, matters or things; and

(vi) the terms and conditions of this Agreement are the result of negotiations between the Parties and that this Agreement will not be construed in favor of or against any Party by reason of the extent to which any Party participated in the preparation of this Agreement.

Section 2. Payment.

In consideration of the mutual releases included in this Agreement and to support AVEO's further Development of the Licensed Antibodies, Novartis will make a one time payment of USD$2.3 million, which will be paid on or before January 2, 2019. For the avoidance of doubt, this payment will not be subject to offset or reduction for any payments previously made by Novartis in connection with the License Agreement. Notwithstanding Section 12.2(i) of the License Agreement, the Material will be transferred to AVEO at no charge.

Section 3. Supply of Material.

Novartis will make available for pick up by AVEO the material and associated documentation identified on *Exhibit A* (the "Material") within [**] after the later of **(i)** the Agreement Effective Date, or **(ii)** the date that AVEO provides all information and data reasonably necessary to transfer the Material in compliance with applicable law and/or cGMP (to the extent applicable); *provided, however*, notwithstanding the foregoing, and to the extent required by cGMP and the Parties' respective Quality Assurance functions, cGMP Material will be transferred only following the execution of a commercially reasonable Quality Agreement between the Parties (as described below). The Material will be transferred Ex Works (Incoterms 2010) and except as provided on *Exhibit A*, is transferred "as is" and without representation or warranty of any kind and Novartis disclaims any implied warranties of merchantability or fitness for a particular purpose with respect to the Material; *provided, however*, that Novartis represents that, with respect to materials manufactured in accordance with cGMP, Novartis handled, stored and transported, and, until it is picked up by AVEO, will continue to handle, store and transport, the Material in accordance with cGMP for biological products. The Parties will enter into a commercially reasonable Quality Agreement with respect to the cGMP Material following the execution of this Agreement. Novartis will share with AVEO all material safety data sheets and customs value information that is reasonably available to Novartis, including without limitation Licensed Antibodies-specific information, as is reasonably necessary to permit AVEO to pick up the Material. AVEO will be solely responsible for any re-testing associated with the Material prior to use. Upon pick up by AVEO, Novartis will have no further obligation to replace lost or damaged material or to provide additional services with respect to such Material.

Section 4. Licenses and Know How Transfer.

(a) Novartis represents and warrants that, as of the Agreement Effective Date, neither it nor any of its Affiliates have filed any patent application or otherwise Control any Patent Rights that claim or cover the Licensed Antibodies or their use.

(b) Novartis and its Affiliates hereby grant to AVEO a perpetual, irrevocable, exclusive, worldwide, fully paid-up license, with the right to grant sublicenses, under all Know-How Controlled by Novartis and its Affiliates and sublicensees as of the Date of Termination, that are specifically related to the Development, manufacture and Commercialization of Products in the Field.

(c) Novartis shall, no later than [**] after the Agreement Effective Date, to the extent permitted by applicable law, complete the transfer to AVEO or its designee, solely for the Development, manufacture and Commercialization of Products in the Field, all right, title, and interest in and to all finalized preclinical and clinical reports and data, and all other supporting data, including pharmacology, toxicology, chemistry and biology data, and documented technical and other information or materials Controlled by Novartis and its Affiliates and sublicensees to the extent related specifically to the Development, manufacture and Commercialization of Products in the Field. Novartis will use commercially reasonable efforts to promptly complete any non-finalized reports, and transfer such reports in final form after completion. Novartis may retain a single copy of all such items for its records as required by applicable law. Novartis will not be required to transfer generalized technologies or SOPs, except to the extent they specifically relate to the Development or Commercialization of Products in the Field.

(d) Novartis represents and warrants that neither it nor any of its Affiliates Control any Regulatory Filings or Regulatory Approvals, or records of any interactions with Regulatory Authorities, related to Products in the Field as of the Date of Termination.

(e) Novartis represents and warrants that it is not a party to any license agreement relating to Licensed Antibodies in the Field (other than this Agreement).

(f) For a period of [**] following the Agreement Effective Date, Novartis will provide such assistance as may be reasonably necessary to transfer manufacturing documents, reports, methods, standards, protocols and materials that are used by Novartis and its Affiliates in the manufacture of the Licensed Antibodies, and cooperate with AVEO in reasonable respects to transfer to AVEO, or AVEO's designated contract manufacturer, the manufacturing technologies (including all relevant Know-How) that are used in the manufacture of the Licensed Antibodies. For the avoidance of doubt, the assistance set forth in this Section 4(f) is limited to interpretation or content of the Novartis Know How that is transferred to AVEO, and in no event will Novartis be required to conduct additional experiments or research in connection with its activities as described in this Section 4(f).

(g) Novartis understands and agrees that the study reports, CMC reports, certificates and other materials and documentation transferred by Novartis hereunder or under the License Agreement may be used in a future IND or other submission to a Regulatory Authority, and agrees to satisfy any reasonable request for documentation or audit in connection with such regulatory submission or by such Regulatory Authority with respect to such studies, reports, certificates, documentation and materials.

(h) The Parties acknowledge that, in connection with the activities described in this Agreement, Novartis will not assign or transfer any agreements that it has with any Third Parties service providers or vendors relating to the Material. At AVEO's request, Novartis will provide a letter of authorization to any such relevant Third Parties informing such Third Parties that the Material is now owned by and in the control of AVEO and authorizing such Third Parties to perform manufacturing, stability and other services on behalf of AVEO with respect to the Material, including authorization for the use and transfer to AVEO of all relevant Know-How related to the Material, pursuant to separate agreements to be negotiated by AVEO and such Third Parties. Following [**] after the Agreement Effective Date, AVEO will have sole responsibility for such Third Party activities.

Section 5. Non-competition.

(a) For a period of three years following the Agreement Effective Date, neither Novartis nor any of its Affiliates will, anywhere in the world, directly or indirectly, Develop, manufacture or Commercialize any anti-GDF15 antagonist antibody or any modified or derivative form of any such antibody, including any active fragment of, pegylated version of (whether or not including amino acid changes) and any other chemically modified versions (including associated amino acid substitutions) of such antibody, and any fused or conjugated versions of any of the foregoing (the "Exclusivity Product") (or license or collaborate with a Third Party to do any of the foregoing) in the Field, except as necessary to perform its obligations hereunder; *provided, however*, that notwithstanding the foregoing, Novartis will retain the right to use the Exclusivity Product for research purposes only.

(b) Novartis represents that, as of the Agreement Effective Date, it and its Affiliates are not engaged and have no plans to engage in the Development or Commercialization of **(a)** any Exclusivity Product, or **(b)** any product for the treatment, prevention or prophylaxis of cachexia, decreased appetite or body weight, which binds to the GDF15 receptor and is a GDF15 antagonist.

Section 6. Indemnity; Limitation of Liability.

(a) Indemnification by AVEO. AVEO will indemnify and hold Novartis, its Affiliates, and their respective officers, directors and employees ("Novartis Indemnitees") harmless from and against any Claims against them to the extent arising or resulting from actions by AVEO, its Affiliates and sublicensees, and their respective employees, agents and subcontractors, in connection with the Development, manufacture or Commercialization of the Licensed Antibodies; *provided, however*, that AVEO will not be obliged to so indemnify, defend and hold harmless the Novartis Indemnitees for any Claims for which Novartis has an obligation to indemnify AVEO Indemnitees pursuant to Section 6(b) or to the extent that such Claims arise from the breach, negligence or willful misconduct of Novartis or the Novartis Indemnitee.

(b) Indemnification by Novartis. Novartis will indemnify and hold AVEO, its Affiliates, and their respective officers, directors and employees ("AVEO Indemnitees") harmless from and against any Claims against them to the extent arising or resulting from the breach of any of the covenants, warranties or representations made by Novartis to AVEO under this Agreement or the License Agreement; *provided, however*, that Novartis will not be obliged to so indemnify, defend and hold harmless the AVEO Indemnitees for any Claims for which AVEO has an obligation to indemnify Novartis Indemnitees pursuant to Section 6(a) or to the extent that such Claims arise from the breach, negligence or willful misconduct of AVEO or the AVEO Indemnitee.

(c) Indemnification Procedure.

(i) For the avoidance of doubt, all indemnification claims in respect of a Novartis Indemnitee or AVEO Indemnitee will be made solely by Novartis or AVEO, respectively.

(ii) A Party seeking indemnification hereunder ("Indemnified Party") will notify the other Party ("Indemnifying Party") in writing reasonably promptly after the assertion against the Indemnified Party of any Claim or fact in respect of which the Indemnified Party intends to base a claim for indemnification hereunder ("Indemnification Claim Notice"), but the failure or delay to so notify the Indemnifying Party will not relieve the Indemnifying Party of any obligation or liability that it may have to the Indemnified Party, except to the extent that the Indemnifying Party demonstrates that its ability to defend or resolve such Claim is adversely affected thereby. The Indemnification Claim Notice will contain a description of the claim and the nature and amount of the Claim (to the extent that the nature and amount of such Claim is known at such time). Upon the request of the Indemnifying Party, the Indemnified Party will furnish promptly to the Indemnifying Party copies of all correspondence, communications and official documents (including court documents) received or sent in respect of such Claim.

(iii) Subject to the provisions of Sections 6(c)(iv) and (v) below, the Indemnifying Party will have the right, upon written notice given to the Indemnified Party within [**] after receipt of the Indemnification Claim Notice to assume the defense and handling of such Claim, at the Indemnifying Party's sole expense, in which case the provisions of Section 6(c)(iv) below will govern. The assumption of the defense of a Claim by the Indemnifying Party will not be construed as acknowledgement that the Indemnifying Party is liable to indemnify any indemnitee in respect of the Claim, nor will it constitute a waiver by the Indemnifying Party of any defenses it may assert against any Indemnified Party's claim for indemnification. In the event that it is ultimately decided that the Indemnifying Party is not obligated to indemnify or hold an Indemnitee harmless from and against the Claim, the Indemnified Party will reimburse the Indemnifying Party for any and all costs and expenses (including attorneys' fees and costs of suit) and any losses incurred by the Indemnifying Party in its defense of the Claim. If the Indemnifying Party does not give written notice to the Indemnified Party, within [**] after receipt of the Indemnification Claim Notice, of the Indemnifying Party's election to assume the defense and handling of such Claim, the provisions of Section 6(c)(v) below will govern.

(iv) Upon assumption of the defense of a Claim by the Indemnifying Party: **(A)** the Indemnifying Party will have the right to and will assume sole control and responsibility for dealing with the Claim; **(B)** the Indemnifying Party may, at its own cost, appoint as counsel in connection with conducting the defense and handling of such Claim any law firm or counsel reasonably selected by the Indemnifying Party; **(C)** the Indemnifying Party will keep the Indemnified Party informed of the status of such Claim; and **(D)** the Indemnifying Party will have the right to settle the Claim on any terms the Indemnifying Party chooses; *provided, however*, that it will not, without the prior written consent of the Indemnified Party, agree to a settlement of any Claim which could lead to liability or create any financial or other obligation on the part of the Indemnified Party for which the Indemnified Party is not entitled to indemnification hereunder or which admits any wrongdoing or responsibility for the claim on behalf of the Indemnified Party. The Indemnified Party will cooperate with the Indemnifying Party and will be entitled to participate in, but not control, the defense of such Claim with its own counsel and at its own expense. In particular, the Indemnified Party will furnish such records, information and testimony, provide witnesses and attend such conferences, discovery proceedings, hearings, trials and appeals as may be reasonably requested in connection therewith. Such cooperation will include access during normal business hours by the Indemnifying Party to, and reasonable retention by the Indemnified Party of, records and information that are reasonably relevant to such Claim, and making the Indemnified Party, the Indemnitees and its and their employees and agents available on a mutually convenient basis to provide additional information and explanation of any records or information provided.

(v) If the Indemnifying Party does not give written notice to the Indemnified Party as set forth in Section 6(c)(iii) or fails to conduct the defense and handling of any Claim in good faith after having assumed such, the Indemnified Party may, at the Indemnifying Party's expense, select counsel reasonably acceptable to the Indemnifying Party in connection with conducting the defense and handling of such Claim and defend or handle such Claim in such manner as it may deem appropriate. In such event, the Indemnified Party will keep the Indemnifying Party timely apprised of the status of such Claim and will not settle such Claim without the prior written consent of the Indemnifying Party, which consent will not be unreasonably withheld. If the Indemnified Party defends or handles such Claim, the Indemnifying Party will cooperate with the Indemnified Party, at the Indemnified Party's request but at no expense to the Indemnified Party, and will be entitled to participate in the defense and handling of such Claim with its own counsel and at its own expense.

(d) Mitigation of Loss. Each Indemnified Party will take and will procure that its Affiliates take all such reasonable steps and action as are necessary or as the Indemnifying Party may reasonably require in order to mitigate any Claims (or potential losses or damages) under this Section 6. Nothing in this Agreement will or will be deemed to relieve any Party of any common law or other duty to mitigate any losses incurred by it.

(e) Limitation of Liability. *NEITHER PARTY NOR ANY OF ITS AFFILIATES SHALL BE LIABLE IN CONTRACT, TORT, NEGLIGENCE BREACH OF STATUTORY DUTY OR OTHERWISE FOR ANY SPECIAL, INDIRECT, INCIDENTAL, PUNITIVE OR CONSEQUENTIAL DAMAGES OR FOR ANY ECONOMIC LOSS OR LOSS OF PROFITS SUFFERED BY THE OTHER PARTY, EXCEPT TO THE EXTENT ANY SUCH DAMAGES ARE REQUIRED TO BE PAID TO A THIRD PARTY AS PART OF A CLAIM FOR WHICH A PARTY PROVIDES INDEMNIFICATION UNDER THIS SECTION 6.*

Section 7. Mutual Release; Non-disparagement.

(a) Release. Each of the Parties, for itself, and on behalf of its officers, directors, employees, agents, Affiliates, and successors and assigns hereby remises, releases and forever discharges the other Party and its officers, directors, employees, agents, Affiliates, and successors and assigns from all claims, suits, actions, charges, demands, judgments, costs and executions present and future, known or unknown, both legal and equitable in any manner arising out of the License Agreement and/or the Development of the Licensed Antibodies; *provided, however*, that notwithstanding anything herein to the contrary, this Agreement shall not remise, release, discharge, terminate, modify, or otherwise cause to expire any obligation or remedy arising under or resulting from Section 14 of the License Agreement. The Parties acknowledge that in executing this Agreement, they have carefully reviewed and had the opportunity to review the terms of this Agreement with counsel of their choice and are fully aware of the extent of their rights and obligations under this Agreement. The Parties further acknowledge that the language of this Agreement shall not be considered as an admission of liability, wrongdoing, or anything improper.

(b) **Non-disparagement**. Subject to applicable law, neither the Parties nor any of their respective officers, directors, employees, agents, Affiliates, and successors and assigns, will in any way publicly disparage, call into disrepute, defame, slander or otherwise criticize the other Party or such other Party's Affiliates officers, directors, employees, agents, Affiliates, or any of their products or services, in any manner that would damage the business or reputation of such other Party or its Affiliates, to the extent related to the License Agreement and/or the Licensed Antibodies.

Section 8. **Confidentiality.**

(a) Subject to the other provisions of this Section 8, all Information disclosed by a Party or its Affiliates under this Agreement will be maintained in confidence and otherwise safeguarded by the recipient Party. The recipient Party may only use the Information for the purposes of this Agreement and pursuant to the rights granted to the recipient Party under this Agreement. Subject to the other provisions of this Section 8, each Party will hold as confidential such Information of the other Party or its Affiliates in the same manner and with the same protection as such recipient Party maintains its own confidential information. Subject to the other provisions of this Section 8, a recipient Party may only disclose Information of the other Party to employees, agents, contractors, consultants and advisers of the Party and its Affiliates and sublicensees and to Third Parties to the extent reasonably necessary for the purposes of, and for those matters undertaken pursuant to, this Agreement; *provided* that such Persons are bound to maintain the confidentiality of the Information in a manner consistent with the confidentiality provisions of this Agreement.

(b) **Exceptions**. The obligations under this Section 8 will not apply to any information to the extent the recipient Party can demonstrate by competent evidence that such information:

(i) is (at the time of disclosure) or becomes (after the time of disclosure) known to the public or part of the public domain through no breach of this Agreement by the recipient Party or its Affiliates;

(ii) was known to, or was otherwise in the possession of, the recipient Party or its Affiliates prior to the time of disclosure by the disclosing Party or any of its Affiliates;

(iii) is disclosed to the recipient Party or an Affiliate on a non-confidential basis by a Third Party who is entitled to disclose it without breaching any confidentiality obligation to the disclosing Party or any of its Affiliates; or

(iv) is independently developed by or on behalf of the recipient Party or its Affiliates, as evidenced by its written records, without reference to the Information disclosed by the disclosing Party or its Affiliates under this Agreement.

Specific aspects or details of Information will not be deemed to be within the public domain or in the possession of the recipient Party merely because the Information is embraced by more general information in the public domain or in the possession of the recipient Party. Further, any combination of Information will not be considered in the public domain or in the possession of the recipient Party merely because individual elements of such Information are in the public domain or in the possession of the recipient Party unless the combination and its principles are in the public domain or in the possession of the recipient Party.

(c) In addition to disclosures allowed under Section 8(a) and 8(b), either Party may disclose Information belonging to the other Party or its Affiliates to the extent such disclosure is necessary in the following instances: **(i)** filing or prosecuting Patent Rights; **(ii)** in connection with Antibodies filings with a Regulatory Authority; **(iii)** prosecuting or defending litigation as permitted by this Agreement; **(iv)** complying with applicable court orders or governmental regulations; **(v)** fulfilling such Party's obligations under the In-licensed AVEO Technology Agreements; or **(vi)** to the extent otherwise necessary or appropriate in connection with exercising the license and other rights granted to it hereunder.

(d) In addition, AVEO may disclose Information of Novartis to Third Parties as may be necessary or useful in connection with the Development, manufacture or Commercialization of the AVEO Antibodies and/or Product(s) on the condition that any such Third Parties agree to be bound by confidentiality and non-use obligations no less rigorous than those contained in this Agreement.

(e) In the event the recipient Party is required to disclose Information of the disclosing Party by law or in connection with bona fide legal process, such disclosure will not be a breach of this Agreement; provided that the recipient Party **(i)** informs the disclosing Party as soon as reasonably practicable of the required disclosure; **(ii)** limits the disclosure to the required purpose; and **(iii)** at the disclosing Party's request and expense, assists in an attempt to object to or limit the required disclosure.

Section 9. Miscellaneous.

(a) **Assignment**. Neither Party may assign its rights and obligations under this Agreement without the other Party's prior written consent, except that either Party may **(i)** assign its rights and obligations under this Agreement or any part hereof to one or more of its Affiliates; or **(ii)** assign this Agreement in its entirety to a successor to all or substantially all of its business or assets to which this Agreement relates. Any permitted assignee will assume all obligations of its assignor under this Agreement (or related to the assigned portion in case of a partial assignment). Any attempted assignment in contravention of the foregoing will be void. Subject to the terms of this Agreement, this Agreement will be binding upon and inure to the benefit of the Parties and their respective successors and permitted assigns.

(b) Extension to Affiliates. Each party will have the right to extend the rights, immunities and obligations granted in this Agreement to one or more of its Affiliates. All applicable terms and provisions of this Agreement will apply to any such Affiliate to which this Agreement has been extended to the same extent as such terms and provisions apply to the Parties hereto. Each party will remain primarily liable for any acts or omissions of its Affiliates.

(c) Severability. Should one or more of the provisions of this Agreement become void or unenforceable as a matter of law, then this Agreement will be construed as if such provision were not contained herein and the remainder of this Agreement will be in full force and effect, and the Parties will use their commercially reasonable efforts to substitute for the invalid or unenforceable provision a valid and enforceable provision which conforms as nearly as possible with the original intent of the Parties.

(d) Governing Law and Jurisdiction. This Agreement will be governed by and construed under the laws of the Commonwealth of Massachusetts, USA, without giving effect to the conflicts of laws provision thereof. The United Nations Convention on Contracts for the International Sale of Goods (1980) will not apply to the interpretation of this Agreement.

(e) Dispute Resolution. Any unresolved disputes between the Parties relating to, arising out of or in any way connected with this Agreement or any term or condition hereof, or the performance by either Party of its obligations hereunder, whether before or after termination of this Agreement, will be resolved by final and binding arbitration. Whenever a Party will decide to institute arbitration proceedings, it will give written notice to that effect to the other Party. Arbitration will be held in Boston, Massachusetts, USA, according to the commercial rules of the International Chamber of Commerce ("ICC"). The arbitration will be conducted by a panel of three arbitrators appointed in accordance with ICC rules; provided that each Party will within [**] after the institution of the arbitration proceedings appoint an arbitrator, and such arbitrators will together, within [**], select a third arbitrator as the chairman of the arbitration panel, each arbitrator will have significant experience in the biopharmaceutical business. If the two initial arbitrators are unable to select a third arbitrator within such [**] period, the third arbitrator will be appointed in accordance with ICC rules. The arbitrators will render their opinion within [**] of the final arbitration hearing. No arbitrator (nor the panel of arbitrators) will have the power to award punitive damages under this Agreement and such award is expressly prohibited; *provided, however*, that the arbiter may, in its discretion, require the losing Party to pay the reasonable costs and expenses of the prevailing party in connection with such arbitration proceeding. Decisions of the panel of arbitrators will be final and binding on the Parties. Judgment on the award so rendered may be entered in any court of competent jurisdiction.

(f) Force Majeure. In the event that either Party is prevented from performing its obligations under this Agreement as a result of any contingency beyond its reasonable control ("Force Majeure"), including but not limited to, any actions of governmental authorities or agencies, war, hostilities between nations, civil commotions, riots, national industry strikes, lockouts, sabotage, shortages in supplies, energy shortages, fire, floods and acts of nature such as typhoons, hurricanes, earthquakes, or tsunamis, the Party so affected will not be responsible to the other Party for any delay or failure of performance of its obligations hereunder, for so long as Force Majeure prevents such performance. In the event of Force Majeure, the Party immediately affected thereby will give prompt written notice to the other Party specifying the Force Majeure event complained of, and will use commercially reasonable efforts to resume performance of its obligations. Notwithstanding the foregoing, if such a Force Majeure induced delay or failure of performance continues for a period of more than three consecutive months, either Party may terminate this Agreement upon written notice to the other Party.

(g) Waivers and Amendments. The failure of any Party to assert a right hereunder or to insist upon compliance with any term or condition of this Agreement will not constitute a waiver of that right or excuse a similar subsequent failure to perform any such term or condition by the other Party. No waiver will be effective unless it has been given in writing and signed by the Party giving such waiver. No provision of this Agreement may be amended or modified other than by a written document signed by authorized representatives of each Party.

(h) Relationship of the Parties. Nothing contained in this Agreement will be deemed to constitute a partnership, joint venture, or legal entity of any type between AVEO and Novartis, or to constitute one as the agent of the other. Moreover, each Party will not construe this Agreement, or any of the transactions contemplated hereby, as a partnership for any tax purposes. Each Party will act solely as an independent contractor, and nothing in this Agreement will be construed to give any Party the power or authority to act for, bind, or commit the other.

(i) **Notices**. All notices, consents, waivers, and other communications under this Agreement must be in writing and will be deemed to have been duly given when: **(a)** delivered by hand (with written confirmation of receipt); or **(b)** when received by the addressee, if sent by an internationally recognized overnight delivery service (receipt requested), in each case to the appropriate addresses set forth below (or to such other addresses as a Party may designate by notice):

If to AVEO:

AVEO Pharmaceuticals, Inc.
One Broadway, 14th Floor
Cambridge, Massachusetts 02142 USA
Attn: Chief Executive Officer

with a required copy to:

AVEO Pharmaceuticals, Inc.
One Broadway, 14th Floor
Cambridge, Massachusetts 02142 USA
Attn: General Counsel

If to Novartis:

Novartis International Pharmaceutical Ltd
Lichtstrasse 35
CH-4056 Basel
Switzerland

with a required copy to:

Novartis Institutes for BioMedical Research, Inc.
250 Massachusetts Avenue
Cambridge, MA 02139 USA
Attn: General Counsel

(j) **Further Assurances.** Novartis and AVEO will execute, acknowledge and deliver any and all such other documents and take any such other action as may be reasonably necessary to carry out the intent and purposes of this Agreement.

(k) **Compliance with Law**. Each Party will perform its obligations under this Agreement in accordance with all applicable laws. No Party will, or will be required to, undertake any activity under or in connection with this Agreement which violates, or which it believes, in good faith, may violate, any applicable law.

(l) Entire Agreement. The provisions of this Agreement are for the sole benefit of the Parties and their successors and permitted assigns, and they will not be construed as conferring any rights to any third party (including any third party beneficiary rights).

(m) Entire Agreement. This Agreement, together with its Exhibits and schedules, sets forth the entire agreement and understanding of the Parties as to the subject matter hereof and supersedes all proposals, oral or written, and all other prior communications between the Parties with respect to such subject matter, with the exception of the surviving provisions of the License Agreement, as described above in Section 6(a).

(n) Cumulative Remedies. No remedy referred to in this Agreement is intended to be exclusive, but each will be cumulative and in addition to any other remedy referred to in this Agreement or otherwise available under law.

[Signature Page Follows]

IN WITNESS WHEREOF, the Parties, intending to be bound, have caused this Agreement to be executed by their duly authorized representatives.

NOVARTIS INTERNATIONAL PHARMACEUTICAL LTD.

By: /s/ Sylvain Beltzung

Name: Sylvain Beltzung

Title: Head Finance NIBR Europe

By: /s/ Gerald Burg

Name: Gerald Burg

Title: BPA Manager NIBR Finance

AVEO PHARMACEUTICALS, INC.

By: /s/ Michael P. Bailey

Name: Michael P. Bailey

Title: President & CEO

Exhibit A

Drug Substance manufacturing

	Clinical batch	**Clinical batch**
Batch Name	[**]	[**]
Date of manufacture	[**]	[**]
Place of manufacture	[**]	[**]
Batch Size	[**]	[**]
Batch type	[**]	[**]
Primary Packaging		
Bottles	[**]	[**]
Composition	[**]	[**]
Current stock	[**]	[**]
Current location	[**]	[**]

Drug Product manufacturing

	Toxicological batch	**Clinical batch**	**Clinical batch**
Batch Name	[**]	[**]	[**]
Date of manufacture	[**]	[**]	[**]
Place of manufacture	[**]	[**]	[**]
Theoretical Batch Size (according CofA)	[**]	[**]	[**]
Drug Substance batch used	[**]	[**]	[**]
Batch type	[**]	[**]	[**]
Primary Packaging			
Vial	[**]		
Stopper	[**]		
Cap	[**]		
Composition	[**]	[**]	[**]
Fill volume	[**]	[**]	[**]
Current stock	[**]	[**]	[**]
Current location	[**]	[**]	[**]

Novartis Reference manufacturing

	[**]
Original DS	[**]
Date of manufacture	[**]
Place of manufacture	[**]
Batch Size	[**]
Release and retest analysis	[**]
Primary Packaging	
Bottles Fill volume	[**]
Composition	[**]
Actual stock*	[**]

***Quantity is subject to change and is current as of Nov 16, 2018. All available stock that is in procession of Novartis to be provided.**

Master Cell Bank

Amount of vials	**Current location**	**Comment**
[**]	[**]	[**]
[**]	[**]	[**]
[**]	[**]	[**]
[**]	[**]	[**]
[**]	[**]	[**]

EXHIBIT 21.1

SUBSIDIARIES OF THE REGISTRANT

Name	Jurisdiction of Organization	Percentage Ownership
AVEO Pharma Limited	United Kingdom	100%
AVEO Securities Corporation	Massachusetts	100%
AVEO Pharma (Ireland) Limited	Ireland	100%

EXHIBIT 23.1

Consent of Independent Registered Public Accounting Firm

We consent to the incorporation by reference in the Registration Statements (Form S-8 Nos. 333-165530, 333-175390, 333-189565 and 333-221838 and Form S-3 Nos. 333-212051, 333-221837 and 333-226190) of AVEO Pharmaceuticals, Inc. of our reports dated March 14, 2019, with respect to the consolidated financial statements of AVEO Pharmaceuticals, Inc. and the effectiveness of internal control over financial reporting of AVEO Pharmaceuticals, Inc., included in this Annual Report (Form 10-K) for the year ended December 31, 2018.

/s/ Ernst & Young LLP

Boston, Massachusetts
March 14, 2019

EXHIBIT 31.1

CERTIFICATION

I, Michael Bailey, certify that:

1. I have reviewed this Annual Report on Form 10-K of AVEO Pharmaceuticals, Inc.;

2. Based on my knowledge, this report does not contain any untrue statement of a material fact or omit to state a material fact necessary to make the statements made, in light of the circumstances under which such statements were made, not misleading with respect to the period covered by this report;

3. Based on my knowledge, the financial statements, and other financial information included in this report, fairly present in all material respects the financial condition, results of operations and cash flows of the registrant as of, and for, the periods presented in this report;

4. The registrant's other certifying officer and I are responsible for establishing and maintaining disclosure controls and procedures (as defined in Exchange Act Rules 13a-15(e) and 15d-15(e)) and internal control over financial reporting (as defined in Exchange Act Rules 13a-15(f) and 15d-15(f)) for the registrant and have:

   (a) Designed such disclosure controls and procedures, or caused such disclosure controls and procedures to be designed under our supervision, to ensure that material information relating to the registrant, including its consolidated subsidiaries, is made known to us by others within those entities, particularly during the period in which this report is being prepared;

   (b) Designed such internal control over financial reporting, or caused such internal control over financial reporting to be designed under our supervision, to provide reasonable assurance regarding the reliability of financial reporting and the preparation of financial statements for external purposes in accordance with generally accepted accounting principles;

   (c) Evaluated the effectiveness of the registrant's disclosure controls and procedures and presented in this report our conclusions about the effectiveness of the disclosure controls and procedures, as of the end of the period covered by this report based on such evaluation; and

   (d) Disclosed in this report any change in the registrant's internal control over financial reporting that occurred during the registrant's most recent fiscal quarter (the registrant's fourth fiscal quarter in the case of an annual report) that has materially affected, or is reasonably likely to materially affect, the registrant's internal control over financial reporting; and

5. The registrant's other certifying officer and I have disclosed, based on our most recent evaluation of internal control over financial reporting, to the registrant's auditors and the audit committee of the registrant's board of directors (or persons performing the equivalent functions):

   (a) All significant deficiencies and material weaknesses in the design or operation of internal control over financial reporting which are reasonably likely to adversely affect the registrant's ability to record, process, summarize and report financial information; and

   (b) Any fraud, whether or not material, that involves management or other employees who have a significant role in the registrant's internal control over financial reporting.

Date: March 14, 2019

/s/ Michael Bailey
Michael Bailey
Chief Executive Officer (Principal Executive Officer)

EXHIBIT 31.2

CERTIFICATION

I, Matthew Dallas, certify that:

1. I have reviewed this Annual Report on Form 10-K of AVEO Pharmaceuticals, Inc.;

2. Based on my knowledge, this report does not contain any untrue statement of a material fact or omit to state a material fact necessary to make the statements made, in light of the circumstances under which such statements were made, not misleading with respect to the period covered by this report;

3. Based on my knowledge, the financial statements, and other financial information included in this report, fairly present in all material respects the financial condition, results of operations and cash flows of the registrant as of, and for, the periods presented in this report;

4. The registrant's other certifying officer and I are responsible for establishing and maintaining disclosure controls and procedures (as defined in Exchange Act Rules 13a-15(e) and 15d-15(e)) and internal control over financial reporting (as defined in Exchange Act Rules 13a-15(f) and 15d-15(f)) for the registrant and have:

   (a) Designed such disclosure controls and procedures, or caused such disclosure controls and procedures to be designed under our supervision, to ensure that material information relating to the registrant, including its consolidated subsidiaries, is made known to us by others within those entities, particularly during the period in which this report is being prepared;

   (b) Designed such internal control over financial reporting, or caused such internal control over financial reporting to be designed under our supervision, to provide reasonable assurance regarding the reliability of financial reporting and the preparation of financial statements for external purposes in accordance with generally accepted accounting principles;

   (c) Evaluated the effectiveness of the registrant's disclosure controls and procedures and presented in this report our conclusions about the effectiveness of the disclosure controls and procedures, as of the end of the period covered by this report based on such evaluation; and

   (d) Disclosed in this report any change in the registrant's internal control over financial reporting that occurred during the registrant's most recent fiscal quarter (the registrant's fourth fiscal quarter in the case of an annual report) that has materially affected, or is reasonably likely to materially affect, the registrant's internal control over financial reporting; and

5. The registrant's other certifying officer and I have disclosed, based on our most recent evaluation of internal control over financial reporting, to the registrant's auditors and the audit committee of the registrant's board of directors (or persons performing the equivalent functions):

   (a) All significant deficiencies and material weaknesses in the design or operation of internal control over financial reporting which are reasonably likely to adversely affect the registrant's ability to record, process, summarize and report financial information; and

   (b) Any fraud, whether or not material, that involves management or other employees who have a significant role in the registrant's internal control over financial reporting.

Date: March 14, 2019

/s/ Matthew Dallas
Matthew Dallas
Chief Financial Officer (Principal Financial Officer)

EXHIBIT 32.1

CERTIFICATION PURSUANT TO 18 U.S.C. SECTION 1350,

AS ADOPTED PURSUANT TO

SECTION 906 OF THE SARBANES-OXLEY ACT OF 2002

In connection with the Annual Report on Form 10-K of AVEO Pharmaceuticals, Inc. (the "Company") for the fiscal year ended December 31, 2018 as filed with the Securities and Exchange Commission on the date hereof (the "Report"), the undersigned, Michael Bailey, Chief Executive Officer of the Company, hereby certifies, pursuant to 18 U.S.C. Section 1350, that, to his knowledge on the date hereof:

(1) The Report fully complies with the requirements of Section 13(a) or 15(d) of the Securities Exchange Act of 1934; and

(2) The information contained in the Report fairly presents, in all material respects, the financial condition and results of operations of the Company.

Date: March 14, 2019

/s/ Michael Bailey
Michael Bailey
Chief Executive Officer (Principal Executive Officer)

EXHIBIT 32.2

CERTIFICATION PURSUANT TO 18 U.S.C. SECTION 1350,

AS ADOPTED PURSUANT TO

SECTION 906 OF THE SARBANES-OXLEY ACT OF 2002

In connection with the Annual Report on Form 10-K of AVEO Pharmaceuticals, Inc. (the "Company") for the fiscal year ended December 31, 2018 as filed with the Securities and Exchange Commission on the date hereof (the "Report"), the undersigned, Matthew Dallas, Chief Financial Officer of the Company, hereby certifies, pursuant to 18 U.S.C. Section 1350, that, to his knowledge on the date hereof:

(1) The Report fully complies with the requirements of Section 13(a) or 15(d) of the Securities Exchange Act of 1934; and

(2) The information contained in the Report fairly presents, in all material respects, the financial condition and results of operations of the Company.

Date: March 14, 2019

/s/ Matthew Dallas
Matthew Dallas
Chief Financial Officer (Principal Financial Officer)