UNITED STATES
SECURITIES AND EXCHANGE COMMISSION
Washington, D.C. 20549

FORM 10-K

☒ **ANNUAL REPORT PURSUANT TO SECTION 13 OR 15(d) OF THE SECURITIES EXCHANGE ACT OF 1934**

For the year ended December 31, 2019

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 001-39069

Aprea Therapeutics, Inc.

(Exact name of registrant as specified in its charter)

Delaware	**84- 2246769**
(State or other jurisdiction of incorporation or organization)	(I.R.S. Employer Identification No.)
535 Boylston Street **Boston, Massachusetts** (Address of principal executive offices)	**02116** (Zip code)

(617) 463-9385
(Registrant's telephone number, including area code)
Not Applicable
(Former name, former address and former fiscal year, if changed since last report)

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

Title of each class	**Trading Symbol**	**Name Of exchange on which registered:**
Common stock, par value $0.001 per share	APRE	NASDAQ Global Select Market

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 whether the registrant is a large accelerated filer, an accelerated filer, a non-accelerated filer, a smaller reporting company, or an emerging growth company. See the 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 ☒

There were 21,054,842 shares of the registrant’s common stock, $0.001 par value, outstanding as of March 27, 2020.

DOCUMENTS INCORPORATED BY REFERENCE

Portions of the registrant’s definitive proxy statement for its 2020 Annual Meeting of Stockholders (the “Proxy Statement”), to be filed within 120 days of the registrant’s fiscal year ended December 31, 2019, are incorporated by reference in Part III of this Annual Report on Form 10-K. Except with respect to information specifically incorporated by reference in this Annual Report on Form 10-K, the Proxy Statement is not deemed to be filed as part of this Annual Report on Form 10-K.

Aprea Therapeutics, Inc.
Annual Report on Form 10-K
For the Year Ended December 31, 2019

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SPECIAL NOTE REGARDING FORWARD-LOOKING STATEMENTS

This Annual Report on Form 10-K includes statements that are, or may be deemed, "forward-looking statements." In some cases, these forward-looking statements can be identified by the use of forward-looking terminology, including the terms "believes," "estimates," "anticipates," "expects," "plans," "intends," "may," "designed," "would," "could," "might," "will," "should," "approximately" or, in each case, their negative or other variations thereon or comparable terminology, although not all forward-looking statements contain these words. They appear in a number of places throughout this Annual Report on Form 10-K and include statements regarding our current intentions, beliefs, projections, outlook, analyses or current expectations concerning, among other things, our ongoing and planned development, commercialization, and market uptake of APR-246 and our other potential product candidates, the strength and breadth of our intellectual property, our ongoing and planned clinical trials, the timing of and our ability to make regulatory filings and obtain and maintain regulatory approvals for our product candidates, the legal and regulatory landscape impacting our business, the degree of clinical utility of our products, particularly in specific patient populations, expectations regarding clinical trial data, our development and validation of manufacturing capabilities, our results of operations, financial condition, liquidity, prospects, growth and strategies, the length of time that we will be able to continue to fund our operating expenses and capital expenditures, our expected financing needs and sources of financing, the industry in which we operate and the trends that may affect the industry or us.

By their nature, forward-looking statements involve risks and uncertainties because they relate to future events, competitive dynamics, and healthcare, regulatory and scientific developments and depend on economic circumstances that may or may not occur in the future or may occur on longer or shorter timelines than anticipated. We caution you that forward-looking statements are not guarantees, or predictive, of future performance and that our actual results of operations, financial condition and liquidity, and the development of the industry in which we operate may differ materially from the forward-looking statements contained in this Annual Report on Form 10-K.

Some of the factors that we believe could cause actual results to differ from those anticipated or predicted include:

- estimates of our expenses, capital requirements and our needs for additional financing;
- the prospects of APR-246 and other product candidates, which are still in development;
- outcome and results of ongoing or future preclinical studies and clinical trials of APR-246;
- the design of our multiple clinical trials, including the sample size, trial duration, endpoint definition, event rate assumptions and eligibility criteria;
- our expectations regarding the timing of data from our Phase 3 and additional clinical trials;
- market acceptance or commercial success of APR-246 and the degree of acceptance among physicians, patients, patient advocacy groups, health care payors and the medical community;
- our expectations regarding competition, potential market size, the size of the patient populations for APR-246, if approved for commercial use, and market acceptance;
- our ability to maintain regulatory approval of APR-246, and any related restrictions, limitations and/or warnings in the label of APR-246;
- the scope of protection we are able to establish and maintain for intellectual property rights covering APR-246;
- potential claims relating to our intellectual property and third-party intellectual property;
- the duration of our intellectual property estate that will provide protection for APR-246;
- developments relating to our competitors and our industry;

- our sales, marketing or distribution capabilities and our ability to commercialize APR-246, if we obtain regulatory approval;
- current and future agreements with third parties in connection with the manufacturing, commercialization, packaging and distribution of APR-246;
- our expectations regarding the ability of our current contract manufacturing partners to produce APR-246 in the quantities and timeframe that we will require;
- our expectations regarding our future costs of goods;
- our ability to generate sufficient or positive preclinical, toxicology, or other in vivo or in vitro data to support the initiation of clinical trials of APR-548;
- business interruptions, including delays in enrollment, patient follow-up and data collection of clinical trials, resulting from epidemic or pandemic disease outbreak, including those related to the novel coronavirus, COVID-19;
- our ability to attract, retain and motivate key personnel and increase the size of our organization;
- our ability to establish collaborations in lieu of obtaining additional financing;
- the impact of government laws and regulations;
- our financial performance; and
- our expectations regarding the time during which we will be an emerging growth company under the JOBS Act or a smaller reporting company under the Exchange Act.

Any forward-looking statements that we make in this Annual Report on Form 10-K speak only as of the date of such statement, and we undertake no obligation to update such statements to reflect events or circumstances after the date of this Annual Report on Form 10-K. You should also read carefully the factors described in the “Risk Factors” included in Part I, Item 1A of this Annual Report to better understand significant risks and uncertainties inherent in our business and underlying any forward-looking statements. As a result of these factors, we cannot assure you that the forward-looking statements in this Annual Report on Form 10-K will prove to be accurate. Furthermore, if our forward-looking statements prove to be inaccurate, the inaccuracy may be material. In light of the significant uncertainties in these forward-looking statements, you should not regard these statements as a representation or warranty by us or any other person that we will achieve our objectives and plans in any specified timeframe, or at all.

This Annual Report on Form 10-K includes statistical and other industry and market data that we obtained from industry publications and research, surveys and studies conducted by third parties. Industry publications and third-party research, surveys and studies generally indicate that their information has been obtained from sources believed to be reliable, although they do not guarantee the accuracy or completeness of such information. While we believe these industry publications and third-party research, surveys and studies are reliable, we have not independently verified such data.

We qualify all of our forward-looking statements by these cautionary statements. In addition, with respect to all of our forward-looking statements, we claim the protection of the safe harbor for forward-looking statements contained in the Private Securities Litigation Reform Act of 1995.

This Form 10-K may include trademarks, tradenames, and service marks that are the property of other organizations. Solely for convenience, our trademarks and tradenames referred to in this Form 10-K may appear without the ® and ™ symbols, but those references are not intended to indicate, in any way, that we will not assert, to the fullest extent under applicable law, our rights, or the right of the applicable licensor to these trademarks and tradenames.

PART I

Item 1. Business

Overview

We are a clinical-stage biopharmaceutical company focused on developing and commercializing novel cancer therapeutics that reactivate mutant p53 tumor suppressor protein. p53 is the protein expressed from the *TP53* gene, the most commonly mutated gene in cancer. We believe that mutant p53 is an attractive therapeutic target due to the high incidence of p53 mutations across a range of cancer types and its involvement in key cellular activities such as apoptosis. Cancer patients with mutant p53 face a significantly inferior prognosis even when treated with the current standard of care, and a large unmet need for these patients remains. Our lead product candidate, APR-246, is a small molecule p53 reactivator that is in late-stage clinical development for hematologic malignancies, including myelodysplastic syndromes, or MDS, and acute myeloid leukemia, or AML. APR-246 has received Breakthrough Therapy, Orphan Drug and Fast Track designations from the FDA for MDS, and Orphan Drug designation from the European Commission for MDS, AML and ovarian cancer, and we believe APR-246 will be a first-in-class therapy if approved by applicable regulators. We have commenced a pivotal Phase 3 trial of APR-246 with azacitidine for frontline treatment of *TP53* mutant MDS. Our pivotal Phase 3 trial is supported by data from two ongoing Phase 1b/2 investigator-initiated trials, one in the U.S. and one in France, testing APR-246 with azacitidine as frontline treatment in *TP53* mutant MDS and AML patients.

In the U.S. Phase 1b/2 trial, sponsored by Dr. David Sallman of the H. Lee Moffitt Cancer Center and Research Institute, or Moffitt, we observed an objective response rate, or ORR, of 88% and a complete remission, or CR, rate of 59% in 41 response-evaluable MDS/AML patients treated with APR-246 and azacitidine, as of November 2019 and as presented at the 2019 American Society of Hematology (ASH) annual meeting. In MDS patients, the CR rate was 61%, with an additional 27% achieving non-CR responses. In AML patients, the CR rate was 50%, with an additional 38% achieving non-CR responses. In addition, 51% of evaluable MDS/AML patients were able to discontinue treatment in order to proceed to allogeneic hematopoietic stem cell transplantation, or allo-HCT. Allo-HCT is currently the only recognized therapy believed to increase the likelihood of long-term survival for *TP53* mutant MDS and AML patients in remission. In the ongoing French Phase 1b/2 trial, sponsored by Groupe Francophone des Myelodysplasies, or GFM, under lead investigator Prof. Pierre Fenaux, we have observed an ORR of 66% and a CR rate of 53% in 38 response-evaluable patients treated with APR-246 and azacitidine, as of December 2019 and as presented and updated at the 2019 American Society of Hematology (ASH) annual meeting. In MDS patients, the CR rate was 59%, with an additional 15% achieving non-CR responses. In AML patients, the CR rate was 44%, with an additional 11% achieving non-CR responses. We expect a final CR endpoint from the French study in the first half of 2020. We expect the results of our pivotal Phase 3 trial and the U.S. and French Phase 1b/2 trials will be submitted in support of marketing applications to the FDA and the European Medicines Agency, or EMA. In addition, we are conducting a Phase 2 trial of APR-246 with azacitidine for the post-allo-HCT maintenance treatment of *TP53* mutant MDS/AML and a Phase 1/2 trial of APR-246 with venetoclax ± azacitidine for the treatment of frontline and relapsed/refractory AML. In the second half of 2020 we expect to commence enrollment in a clinical trial for the treatment of *TP53* mutant non-Hodgkin lymphomas (NHL); and a clinical trial in relapsed/refractory gastric, bladder and non-small cell lung cancers. We are also developing a next-generation small molecule p53 reactivator, APR-548, for potential use in multiple hematologic malignancies and other oncologic indications, and expect to file an IND with the FDA in the first half of 2020. We have assembled a management team with extensive experience in the discovery, development and commercialization of novel oncology drugs to support our mission of developing p53-reactivating therapies for cancer patients.

Our lead programs are summarized below. We currently retain global development and commercialization rights to all of our product candidates:

(1) Investigator-initiated trial

(2) With or without azacitidine

We believe that targeting p53 and thereby reactivating key intrinsic cellular functions has the potential to significantly impact patients' lives and treatment strategies for a wide variety of cancers. p53 is a tumor suppressor protein that in its normal state functions to sense DNA damage and induce cell cycle arrest, DNA damage repair, senescence and cellular apoptosis. Mutant p53 is an attractive target because it is widely mutated across hematologic and solid tumors and is associated with an aggressive clinical and molecular phenotype. In preclinical studies and clinical trials, mutations in p53 and the apoptotic pathway have been shown to play a key role in cancer genesis, proliferation and resistance to currently marketed therapeutic agents. Many approved and clinical stage oncology drugs are more effective with a functional p53 pathway. Our approach is to restore normal function to p53, thereby re-enabling a cell's ability to undergo apoptosis. Accordingly, we believe that by targeting p53, our drug candidates may enhance the ability of other anti-cancer therapies to induce cancer cell death. In addition, we believe that our approach may counteract resistance mechanisms that characterize many of the most aggressive cancers. Although we have observed single agent activity in preclinical testing of APR-246, our current clinical program is focused on combination therapy based on the strong additive or synergistic effects we have observed in combination with multiple conventional chemotherapeutic drugs, DNA hypomethylating agents, or HMAs, inhibitors of anti-apoptotic proteins and immuno-oncology checkpoint blockade agents.

Our lead product candidate, APR-246, is a small molecule that has demonstrated reactivation of mutant p53 in clinical trials. Promising clinical data support the application of APR-246 across a variety of hematologic malignancies and other oncologic indications. APR-246 is a pro-drug that is administered intravenously and forms the active moiety, 2-methylene-quinuclidin-3-one, or MQ, under physiological conditions. APR-246 has been shown to induce apoptosis in cancer cells with mutant p53 in Phase 1/2 trials. We believe the mechanism of action and current adverse event profile of APR-246 may provide the basis for its combination with both conventional and novel therapies, such as targeted

therapies, chemotherapy, radiotherapy and immuno-therapy. APR-246 has received Breakthrough Therapy, Orphan Drug and Fast Track designations from the FDA for MDS, and Orphan Drug designation from the European Commission for MDS, AML and ovarian cancer. We recently secured *eprenetapopt* as the international nonproprietary name for APR-246.

We are conducting, supporting and planning multiple clinical trials of APR-246:

- **Pivotal Phase 3 MDS Trial—**We are currently enrolling a pivotal Phase 3 randomized, controlled trial evaluating APR-246 with azacitidine as frontline therapy in HMA-naïve *TP53* mutant MDS patients. The trial has a target enrollment of 154 patients randomized in a 1:1 ratio to either the azacitidine control arm or to the APR-246 + azacitidine experimental arm, with a primary endpoint of CR rate. The first patient was enrolled in January 2019 and we had anticipated full enrollment in our Phase 3 trial in the first quarter of 2020 and top-line data from this trial in the second half of 2020. We have observed a recent decrease in both patient screening and patient enrollment as a result of the recent coronavirus *(COVID-19)* pandemic. Together with our investigators and clinical sites, we are assessing the potential impact of the coronavirus pandemic on enrollment and the ability to maintain patients enrolled in this trial, and the corresponding impact on the timing of the completion of the trial and subsequent availability of top-line data.

- **U.S. Phase 1b/2 MDS/AML Trial—**We are supporting an investigator-initiated Phase 1b/2 single-arm, open-label trial in the United States, sponsored by Dr. David Sallman of the H. Lee Moffitt Cancer Center and Research Institute, or Moffitt, evaluating APR-246 with azacitidine as frontline therapy in HMA-naïve patients with *TP53* mutant MDS or AML. We are collaborating with Moffitt on this trial by supplying APR-246, in addition to providing financial support. The primary endpoint of the trial is CR rate and enrollment was completed with 55 patients. The regimen achieved an ORR of 88% and a CR rate of 59% in 41 response-evaluable patients as of November 2019. In MDS patients, the CR rate was 61%, with an additional 27% achieving non-CR responses. In AML patients, the CR rate was 50%, with an additional 38% achieving non-CR responses. In addition, 51% of evaluable MDS/AML patients were able to discontinue treatment in order to proceed to allo-HCT. With a median follow-up of 10.8 months, the median duration of response was 8.0 months (95% confidence interval: 6.5 – 11.2 months). The median duration of CR was 7.3 months (95% confidence interval: 7.3 – not estimable months) in MDS patients and 7.0 months (95% confidence interval: 3.3 – not estimable months) in AML patients. By intention to treat analysis, median OS was 10.8 months (95% confidence interval: 8.1 − 13.4 months) with significantly prolonged OS of 13.7 months (95% confidence interval: 10.8 – 16.5 months) in responding patients versus 3.9 months (95% confidence interval: 1.9 – 6.0 months) in non-responding patients ($p < 0.0001$). Analysis of peer-reviewed published data in *TP53* mutant MDS and AML suggests frontline azacitidine monotherapy provides an ORR of 40-50% for AML, CR rates of approximately 20% and median OS of 7-8 months.

- **French Phase 1b/2 MDS/AML Trial—**We are supporting a parallel investigator-initiated Phase 1b/2 single-arm, open-label trial in France, sponsored by Groupe Francophone des Myelodysplasies, or GFM, under lead investigator Prof. Pierre Fenaux, evaluating APR-246 with azacitidine as frontline therapy in HMA-naïve patients with *TP53* mutant MDS or AML. We are collaborating with GFM on this trial by supplying APR-246, in addition to providing financial support. The primary endpoint of the trial is CR rate and enrollment has completed with 53 patients. As of December 2019, the regimen has achieved an ORR of 66% and CR rate of 53% in 38 response-evaluable patients. In MDS patients, the CR rate was 59%, with an additional 15% achieving non-CR responses. In AML patients, the CR rate was 44%, with an additional 11% achieving non-CR responses. Top-line results on the CR rate primary endpoint are expected in the first half of 2020. Responding patients who proceed to allo-HCT are eligible to continue receiving APR-246 with azacitidine as post-transplant maintenance therapy.

- **Phase 2 MDS/AML Post-Transplant Trial—**We are currently enrolling our single-arm, open-label Phase 2 trial evaluating APR-246 with azacitidine as post-transplant maintenance therapy in *TP53* mutant MDS and AML patients who have received allo-HCT. The primary endpoint is relapse-free survival at 12 months. Target enrollment is 31 patients and we had anticipated full enrollment in the first half of 2020.

Together with our investigators and clinical sites, we are assessing the potential impact of the coronavirus pandemic on enrollment and the ability to maintain patients enrolled in this trial. Analysis of the historical, peer-reviewed published data in *TP53* mutant MDS and AML patients who undergo bone marrow transplant suggests that *TP53* mutation is associated with a 4-fold increased risk of death following transplantation and a 1-year relapse-free survival of only 30%.

- **Phase 1 AML Trial—**Based on *in vitro* data evidencing synergistic activity between APR-246 and a Bcl-2 inhibitor, we are conducting a Phase 1 clinical trial in frontline and relapsed/refractory *TP53* mutant AML assessing APR-246 with venetoclax with or without azacitidine. The primary endpoint is the composite rate of CR and CR with incomplete hematologic recovery, or CRi. Together with our investigators and clinical sites, we are assessing the potential impact of the coronavirus pandemic on enrollment and the ability to maintain patients enrolled in this trial. Analysis of the peer-reviewed published data in *TP53* mutant AML patients suggests that the regimen of venetoclax with azacitidine provides CR/CRi of 45-50% and median OS of 6-7 months.

- **Phase 1/2 NHL Trial—**As further assessment of APR-246 in hematological malignancies, we have designed and plan to conduct a Phase 1/2 clinical trial in relapsed/refractory *TP53* mutant chronic lymphoid leukemia (CLL) and mantle cell lymphoma (MCL) assessing APR-246 with venetoclax and rituximab, and APR-246 with ibrutinib. We are targeting the first patient to be enrolled in the second half of 2020.

- **Phase 1/2 Solid Tumor Trial—**Based on *in vitro* data evidencing synergistic activity between APR-246 and immuno-therapy agents including anti-PD-1 antibody, we have designed and plan to conduct a Phase 1/2 clinical trials in relapsed/refractory gastric, bladder and non-small cell lung cancers assessing APR-246 with anti-PD-1 therapy. We are targeting the first patient to be enrolled in the second half of 2020.

Our second product candidate, APR-548, is a next-generation p53 reactivator with the potential for oral administration. APR-548 is a unique analog of APR-246 and therefore a pro-drug of MQ. APR-548 exhibits high oral bioavailability in preclinical testing and is being developed in an oral dosage form. We are currently conducting Investigational New Drug, or IND, enabling preclinical studies of APR-548 and are targeting submission of an IND in the first half of 2020.

We have assembled an outstanding team, which includes world-class scientific and clinical oncology leaders, to execute on our mission to create novel p53-reactivating therapies to help patients suffering with cancer. Together with our board of directors, our scientific founders and members of our management team have significant experience in drug discovery and development and finance. Collectively, we believe our team's strong capabilities position us to build a leading biotech company focused on developing novel cancer therapies to address the significant unmet medical need of patients with p53 mutant malignancies, for whom there are limited effective therapeutic options.

Our strategy

Our mission is to be the leading player in the development and commercialization of p53-targeted cancer therapies. The key elements of our strategy are to:

- ***Rapidly develop and commercialize our lead mutant p53 reactivator, APR-246, in frontline combination therapy for TP53 mutant MDS.*** We are currently advancing APR-246 with azacitidine through Phase 3 clinical development in *TP53* mutant MDS. We are initially targeting frontline *TP53* mutant MDS, where there are few approved therapies, no approved p53-targeted therapies and a continued high unmet medical need. We believe the data generated to date support compelling clinical activity in this underserved patient population.

- ***Expand the clinical opportunity for APR-246 by pursuing development of combination therapy for post-transplant maintenance in TP53 mutant MDS and AML.*** Allo-HCT is currently considered the only curative option for patients with *TP53* mutant MDS/AML, and even with transplantation the outcomes for these patients remain poor. We are currently advancing APR-246 as post-transplant maintenance therapy in *TP53* mutant MDS and AML in the French Phase 1b/2 MDS/AML Trial and our Phase 2 MDS/AML

Post-Transplant Trial. We believe that this approach may offer an opportunity to quickly expand the commercial potential of APR-246.

- ***Rapidly develop APR-246 for frontline and relapsed/refractory TP53 mutant AML.*** We are currently advancing the clinical development of APR-246 in frontline *TP53* mutant AML through the U.S. Phase 1b/2 MDS/AML Trial and the French Phase 1b/2 MDS/AML Trial. While these frontline trials are evaluating APR-246 with azacitidine, we are also evaluating APR-246 with venetoclax with or without azacitidine in both frontline and relapsed/refractory AML patients. We believe that the treatment of these patients may offer an opportunity to significantly expand the commercial potential of APR-246.

- ***Advance our next-generation p53 reactivator, APR-548.*** We are developing a next-generation small molecule p53 reactivator with the potential to be delivered in an oral dosage form. We intend to initially develop APR-548 in *TP53* mutant MDS/AML. We believe that an oral p53-reactivating drug will improve patient convenience and compliance, if approved, including for patients receiving prolonged therapy in the maintenance setting.

- ***Explore additional oncology indications for APR-246 and APR-548.*** We are evaluating combination treatment with our product candidates in additional hematologic and solid tumor indications where mutant and dysfunctional p53 is a driver of disease. We have preclinical models that show synergistic effects of APR-246 with a variety of anti-cancer agents including multiple conventional chemotherapeutic drugs, HMAs, inhibitors of anti-apoptotic proteins and immuno-oncology checkpoint blockade agents. Based on our preclinical data, we believe there is potential to expand APR-246 and APR-548 into additional oncological indications.

- ***Maximize the commercial opportunity of our product candidates across global markets.*** We currently retain worldwide development and commercialization rights to all our product candidates. We intend to retain commercial rights to our product candidates in the United States and may elect to build a focused commercial oncology organization to market any of our product candidates that are approved. Outside of the United States, we may elect to selectively evaluate strategic partnership opportunities for our product candidates with partners whose development and commercial capabilities complement our own.

Our approach

Background on p53, a key tumor suppressor protein

TP53 is the most widely mutated gene in human cancers. Since its discovery in 1979, p53 has been extensively studied by researchers and the pharmaceutical industry due to its central role in preventing the initiation and progression of liquid and solid tumors. p53 has long been referred to as “the guardian of the genome” because it is the body’s first line of cellular defense against cancers. Among its multiple biologic functions, p53 regulates a variety of tumor suppressive responses including cell cycle arrest, DNA repair, apoptosis, and senescence.

p53 is activated when DNA damage is detected and when oxidative or other cellular stresses exceed thresholds for normal cellular function. The result of p53 activation is to facilitate the repair of the cell or trigger killing of the damaged cell, through a process known as apoptosis, before it can become cancerous and replicate. Given that the mutational status of p53 in a tumor has a strong impact on sensitivity to commonly used anti-cancer drugs and radiotherapy, p53 is important both as clinical marker and as a novel therapeutic target. Importantly, mutations in p53 not only diminish tumor suppression function but also often lead to the acquisition of new pro-tumor functions.

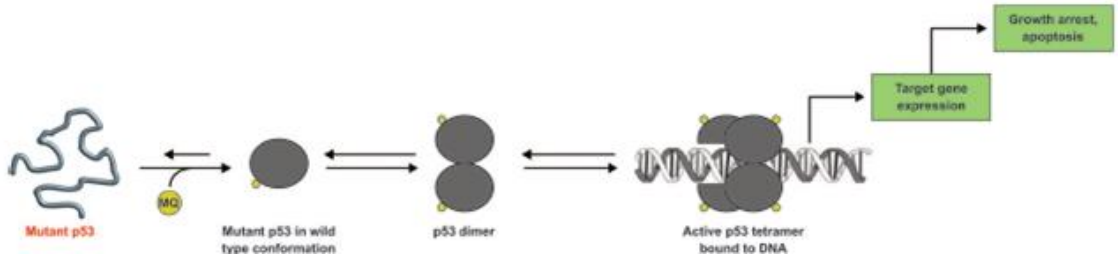
To date, more than 25,000 unique *TP53* mutations have been reported and thus a key challenge in the development of p53-targeted therapies is the vast number of mutations that compromise tumor suppression activity. Incidence of *TP53* mutations increases after treatment with chemotherapy or radiation. The most common of these are missense mutations, involving the site-specific exchange of one amino acid for another, and account for 75% of all p53 mutations; however, even the six most frequently mutated “hotspot” missense mutations in p53 collectively represent only ~30% of all missense mutations. Therefore, we believe that a therapeutic agent that targets a small subset of *TP53* mutations would

be of limited benefit. To circumvent these challenges, previous drug development efforts have primarily focused on gene therapy delivery of wild type p53 or drugs that disrupt interaction with proteins that control p53 activation and abundance. We believe the more effective approach is our direct conformational reactivation of mutant p53 and restoration of wild-type structure and activity, independent of the type of mutation.

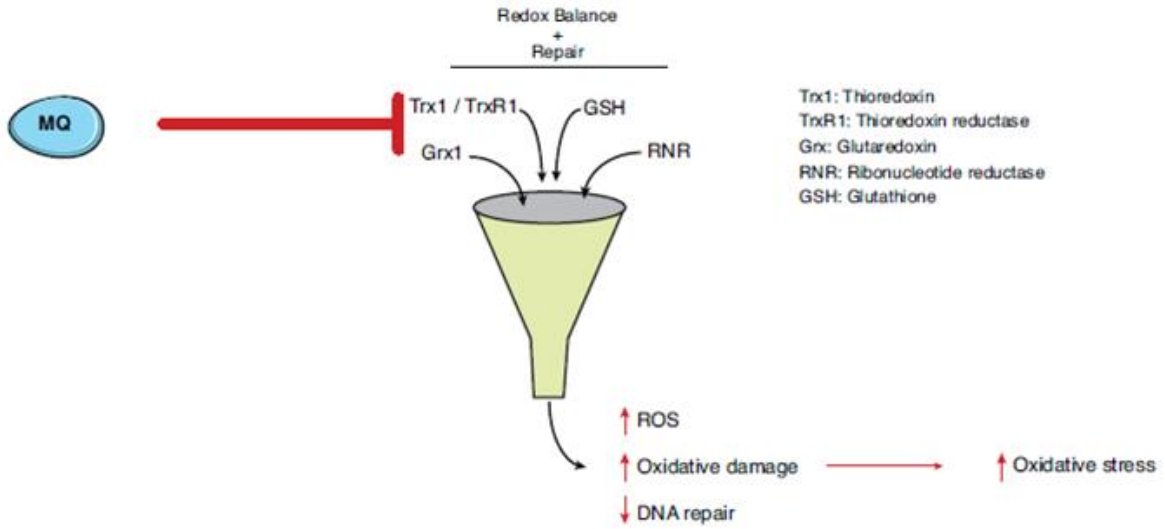
Our approach to re-activating p53

One of the most attractive features of apoptosis activation as a cancer therapy is its potential to induce tumor regression rather than to simply stop tumor growth. However, pro-apoptotic agents that cannot discriminate between malignant and normal cells carry a significant risk of side effects. This is an important issue with traditional cancer treatments: radiotherapy and chemotherapy induce apoptosis only as a secondary effect of the cellular damage they induce. These treatments affect most proliferating cells without distinction between malignant or normal cells. Our product candidates, in contrast, are designed to reactivate mutant, non-functional p53 to restore normal apoptotic functions in cancer cells without triggering apoptosis in normal cells, thereby selectively enhancing the effects of other chemotherapy drugs in malignant cancer cells with mutant p53.

APR-246 and the MQ, have been extensively studied. MQ-modified mutant p53 protein has been shown to induce significant levels of apoptosis, indicating that covalent binding of MQ activates mutant p53 and induces a p53-dependent apoptotic response. Experiments by our founders looking directly at the conformational state of p53 protein in cells have confirmed that binding of MQ stabilizes mutant p53 in the functional, wild type conformation. Structural biology studies performed by our collaborators have produced the first-ever crystal structures of several single-site missense mutant p53 forms bound to DNA. These structures confirm both the sites of MQ binding to mutant p53 and the stabilization of mutant p53 by MQ in the wild type conformation. Reactivation of mutant p53 via stabilization of the properly folded wild type conformation is the key step in our product candidates' mechanism of action. The following diagram illustrates this mechanism.



In *in vitro* and *in vivo* experiments, our lead p53 re-activating product candidate, APR-246, via MQ, impaired tumor cells' capacity to respond to oxidative stress. In parallel to binding mutant p53, and as published by Liu et al, Nat Commun, 2017, 14844, MQ depletes intracellular glutathione, or GSH, and induces reactive oxygen species, or ROS. Furthermore, as published in Peng et al, Cell Death Dis, 2013, e881, MQ has been shown to inhibit the reductase activities of the redox enzyme thioredoxin reductase, or TrxR1, and convert the enzyme to a dedicated oxidase, thereby increasing levels of ROS. Additional results reported in Haffo et al, Sci. Reports, 2018, 12671, have demonstrated MQ inhibition of thioredoxin, or Trx1, and glutaredoxin, or Grx1, which further augment oxidative stress, and ribonucleotide reductase, or RNR, which decreases the cell's ability to repair damaged DNA. These effects on the cellular redox system, illustrated in the following diagram, may contribute to the anticancer activity of APR-246 as well as the selectivity for effects on cancer cells versus healthy normal cells. Malignant cells have higher levels of ROS than healthy cells and are thus more susceptible to increased stress that can trigger pro-apoptotic responses. MQ-induced oxidative stress is therefore an important secondary feature of the mechanism of action.



Cell fate is a function of the extent and severity of cellular stresses, such as oxidative stress and DNA damage. A network of proteins translates information about cellular stress into biochemical signals and relays this information back to p53, the center of the network. p53 integrates these biochemical signals and becomes activated to initiate cell cycle arrest. When cellular stress and damage are sufficiently high, such as with chemotherapy, p53 initiates apoptosis. MQ restores the ability of a cell to respond to oxidative stress and DNA damage via reactivation of mutant p53 and induces heightened oxidative stress signals to which reactivated p53 can respond. The overlap of these features of the mechanism of action may in turn provide more efficient induction of apoptosis.

Market opportunity for p53 re-activating product candidates

We believe there is a significant market opportunity for therapies targeting mutant p53 because these mutations occur in more than half of all tumors and confer an inferior prognosis relative to patients with wild type p53. Preclinical anti-tumor activity has been observed with APR-246 in a wide variety of hematological and solid tumor models and cell lines as reviewed and referenced in Perdrix et al, Cancer 2017, 9, 172. Given the importance of p53 mutations as disease-driver mutations, the sensitivity of hematopoietic cells to oxidative stress and continued unmet medical need, we are initially focused in our clinical development on hematological malignancies, MDS and AML, with *TP53* mutations.

Myelodysplastic syndromes—disease background and opportunity

MDS is a collection of bone marrow disorders in which malignant hematopoietic cells prevent production of healthy, mature blood cells. Low blood cell counts, called cytopenias, are a hallmark feature of MDS and are a principal cause of morbidity and mortality from infection and bleeding. MDS can develop *de novo* or may arise secondary to chemotherapy or radiation treatment for a different, prior malignancy or following an antecedent hematological disorder. Treatment-related MDS is associated with increased complex chromosomal abnormalities and carries a worse prognosis than *de novo* MDS. As of 2019, there are an estimated 200,000 MDS patients worldwide, with 68,000 of these in the United States and 69,000 MDS patients across the five major markets of the European Union and Japan. Globally, MDS prevalence is expected to increase 2-3% annually in mature markets and 3-4% annually in emerging markets as populations age. MDS predominantly affects older adults, with approximately 75% of patients aged 60 years or older at diagnosis. Around 30% of patients diagnosed with MDS will progress to AML, with the rate being higher for patients with more advanced disease.

MDS patients are segmented into different risk groups according the number of cytopenias, bone marrow blast percentage, and cytogenetic abnormalities. The presence of three or more coincident structural genetic abnormalities is

classified as a complex karyotype, which correlates with poor prognosis, low response to intensive chemotherapy, high rate of relapse and inferior survival. Mutations in *TP53* occur in approximately 20% of patients with *de novo* MDS and in more than 30% of patients with therapy-related MDS who develop disease secondary to chemotherapy or radiation treatment for other cancers. Sequencing of a panel of commonly mutated genes, including *TP53*, is standard practice in the diagnosis of MDS.

Historically, treatment response rates in *TP53* mutant MDS patients have been poor regardless of therapy. Treatment with azacitidine is the standard of care for frontline therapy in *TP53* mutant MDS, with ORR of 40-45%, a CR rate of 20% or less and median OS of approximately 7-8 months. There are no established curative pharmacologic therapies for MDS. Allo-HCT is currently the only recognized therapy believed to increase the likelihood of long term survival for *TP53* mutant MDS patients; however, many patients are not candidates for allo-HCT due to lack of sufficient clinical response to initial therapy, advanced age, comorbidities or lack of a suitable donor. Unfortunately, even for those *TP53* mutant MDS patients who receive allo-HCT, the post-transplantation prognosis is poor: *TP53* mutations are associated with a 4-fold increased risk of death and 1-year relapse-free survival of only 30% following transplantation.

Given the poor prognosis for patients with *TP53* mutant MDS there is a significant need for more effective therapies in this population, particularly if such treatments have a favorable safety profile, a mechanism of action that targets mutant p53 directly, and may be used in combination with existing or future treatment options.

Acute myeloid leukemia—disease background and opportunity

AML is the most common form of adult leukemia, with the highest incidence in patients aged 60 years and older. AML is characterized by proliferation of abnormal immature white blood cells which, like MDS, impairs production of normal blood cells. AML can develop *de novo* or may arise secondary to progression of other hematologic disorders or from chemotherapy or radiation treatment for a different, prior malignancy; secondary AML carries a worse prognosis than *de novo* AML. As of 2019, there are an estimated 213,000 AML patients worldwide, with 37,000 of these in the United States and 41,000 across the five major European Union markets and Japan. Globally, AML prevalence is expected to increase approximately 1-2% annually in mature markets and 2-3% in emerging markets.

AML patients are segmented into different risk groups according to cytogenetic abnormalities. The presence of three or more coincident structural genetic abnormalities is classified as a complex karyotype, which correlates with adverse prognosis, low response to intensive chemotherapy, high rate of relapse and inferior survival. Mutations in *TP53* occur in approximately 20% of patients with newly diagnosed AML, more than 30% of patients with therapy-related AML and approximately 70-80% of patients with complex karyotype. Sequencing of a panel of commonly mutated genes, including *TP53*, is standard practice in the diagnosis of AML.

Historically, treatment response rates in *TP53* mutant AML patients have been poor regardless of therapy. Treatment with azacitidine is the standard of care therapy for frontline therapy in *TP53* mutant AML, with 40-50% ORR, 10-20% CR rate and OS of 7-8 months. Treatment of relapsed/refractory AML with venetoclax and azacitidine provides 40-50% ORR and OS of ~7 months. Similar to MDS, allo-HCT is currently the only recognized therapy believed to increase the likelihood of long term survival for *TP53* mutant AML patients; however, many patients are not candidates for allo-HCT due to lack of sufficient clinical response to therapy, advanced age, comorbidities or lack of a suitable donor. Unfortunately, even for those *TP53* mutant AML patients who receive allo-HCT, the post-transplantation prognosis is poor: *TP53* mutations are associated with a 4-fold increased risk of death and 1-year relapse-free survival of only 30% following transplantation.

Given the poor prognosis for patients with *TP53* mutant AML there is a significant need for more effective therapies in this population, particularly if such treatments have a favorable safety profile, a mechanism of action that targets mutant p53 directly, and may be used in combination with existing or future treatment options.

Chronic lymphocytic leukemia—disease background and opportunity

Chronic lymphocytic leukemia (CLL) is one of the most common types of B-cell non-Hodgkin lymphoma (NHL), characterized by a progressive accumulation of functionally incompetent monoclonal lymphocytes. As of 2017, the

estimated prevalence of CLL was approximately 205,000 in the United States and approximately 180,000 across the five major European Union markets and Japan.

CLL is associated with a highly heterogeneous disease course that is partly explained by the diverse genetic aberrations identified in CLL patients. Deletions in chromosome 17p [del(17p)] and *TP53* mutations belong to the strongest prognostic and predictive markers guiding treatment decisions in CLL. Del(17p) results in loss of one copy of the *TP53* gene and is often accompanied by mutation in the remaining *TP53* gene copy. *TP53* mutation occurs in approximately 25% of CLL and up to approximately 85% of del(17p) CLL. *TP53* mutant CLL and del(17p) CLL are associated with markedly decreased survival and impaired response to chemoimmunotherapy. Recently, new targeted therapies have become available for the treatment of del(17p) CLL, including the Bruton tyrosine kinase (BTK) inhibitor, ibrutinib, and the Bcl-2 inhibitor, venetoclax. In R/R del(17p) CLL patients, ibrutinib has been reported to achieve 85% ORR and 11% CR/CRi, with an estimated PFS and OS at 24 months of 65% and 77%, respectively. In R/R del(17p) CLL patients, venetoclax has been reported to achieve 77% ORR and 20% CR/CRi, with an estimated PFS and OS at 24 months of 54% and 73%, respectively. Patients treated with venetoclax who had received ibrutinib in a prior line of therapy achieved 63% ORR and 13% CR/CRi, with a 24-month PFS and OS of 50% and 55%, respectively. Although these newer therapeutic options have improved outcomes for patients with *TP53* mutant / del(17p) R/R CLL, the data indicate that many patients will ultimately relapse and die from their disease.

Mantle cell lymphoma—disease background and opportunity

Mantle cell lymphoma (MCL) is an aggressive form of NHL that accounts for approximately 6% of all NHL cases. It is characterized by accumulation of malignant B lymphocytes in the outer edge, or mantle zone, of lymph node follicles. As of 2017, the estimated prevalence of MCL was approximately 16,000 in the United States and approximately 16,000 across the five major European Union markets and Japan.

There are two major variants of MCL, known as classical and leukemic non-nodal (L-NN). Classical nodal MCL, accounting for 80-90% of cases, affects the lymph nodes and extra nodal sites. In contrast, L-NN MCL involves the bone marrow, peripheral blood and spleen. Of these, classical MCL is the more aggressive disease. Like CLL, del(17p) and *TP53* mutation are the most frequent findings in MCL. *TP53* mutations occur in approximately 20% of cases and are associated with poor prognosis and resistance to first-line and later-line regimens. Ibrutinib is a preferred treatment option for R/R MCL patients but response rates and outcomes are significantly inferior for *TP53* mutant versus *TP53* wild-type: 55% vs 70% ORR; 0% vs 25% CR; 4.0 months vs 12.0 months PFS; and 10.3 months vs 33.6 months OS. Patients who are refractory to, or relapse after treatment with, ibrutinib have limited treatment options. Venetoclax treatment of patients having R/R MCL following ibrutinib is being tested; available data show 53% ORR, 18% CR, median PFS of 3.2 months and median OS of 9.4 months; however, analysis of *TP53* mutant versus wild-type has not been reported. Although these newer therapeutic options have improved outcomes for patients with *TP53* mutant / del(17p) R/R MCL, the data indicate that many patients will ultimately relapse and die from their disease.

Gastric cancer—disease background and opportunity

Gastric cancer includes cancers of the stomach and gastroesophageal junction. It is the fifth most common cancer worldwide and the third leading cause of cancer-related death. In 2020, the estimated prevalence of gastric cancer is approximately 45,000 in the United States, approximately 90,000 in the five major European Union markets and approximately 350,000 in Japan.

Gastric cancer is typically detected at an advanced stage. *TP53* mutation occurs in approximately 35%-55% of gastric cancers. Disease progression after first-line chemotherapy is common. Therapeutic options are limited for patients whose disease progresses after two or more lines of treatment. The humanized anti-PD-1 monoclonal antibody, pembrolizumab, is approved by the US FDA for the treatment of patients with recurrent gastric cancer after two or more prior lines of therapy, including fluoropyrimidine- and platinum-containing chemotherapy and, if appropriate, HER2/new-targeted therapy, and whose tumors express PD-L1. In patients with PD-L1 positive tumors who had received two prior lines of therapy, pembrolizumab achieved 22.7% ORR, 2.7% CR, and a median duration of response of 8.1 months.

Bladder cancer—disease background and opportunity

Bladder cancer is a common cancer worldwide and is more common in men than in women. In 2018, the estimated prevalence of bladder cancer was approximately 275,000 in the United States, approximately 370,000 in the five major European Union markets and approximately 120,000 in Japan.

TP53 mutation occurs in approximately 50% of bladder cancer cases. First-line treatment with platinum agents is standard of care; however, few therapeutic options exist for second-line treatment of patients with platinum-refractory bladder cancer. The humanized anti-PD-1 monoclonal antibody, pembrolizumab, is approved by the US FDA for the treatment of locally advanced or metastatic, PD-L1 positive bladder cancer who are not eligible for cisplatin-containing chemotherapy; in patients who are not eligible for any platinum-containing chemotherapy, regardless of PD-L1 status; and in patients who have disease progression during or following platinum-containing chemotherapy. In eligible patients, pembrolizumab achieved 21.1% ORR, 9.3% CR, and median OS of 10.3 months.

Non-small cell lung cancer—disease background and opportunity

Lung cancer is the most common cancer worldwide and the leading cause of cancer-related death. Non-small cell lung cancer (NSCLC) is the most common type of lung cancer, accounting for 84% of all lung cancer diagnoses. In 2019, the estimated prevalence of NSCLC was approximately 312,000 in the United States, 194,000 in the five major European Union markets and approximately 312,000 in Japan.

TP53 mutation occurs in up to 80% of NSCLC cases. The humanized anti-PD-1 monoclonal antibody, pembrolizumab, is approved by the US FDA as a single agent in NSCLC for the first-line treatment of PD-L1 positive metastatic disease or in patients who have progressive disease during or following platinum-containing chemotherapy. As first-line treatment of eligible patients with high PD-L1 expression, pembrolizumab achieved 45% ORR, 4% CR, and median OS of 30 months. In patients with previously treated NSCLC, pembrolizumab achieved 19% ORR, 0% CR and median OS of 12.7 months. Treatment options are limited for patients whose disease is R/R to prior anti-PD-1 therapy.

Our lead product candidate, APR-246

Our lead product candidate, APR-246, is a small molecule that has demonstrated reactivation of mutant p53 in both clinical trials and preclinical studies. Promising clinical and preclinical data support the application of APR-246 across a variety of hematologic malignancies and other oncologic indications. Based on its mechanism of action of p53 reactivation and the complementary increase in oxidative stress, as well as its established synergy with anti-cancer agents as evidenced in preclinical studies, APR-246 treatment may be effective in a broad range of clinical settings.

Clinical trials of APR-246 in hematologic malignancies

We are currently evaluating APR-246 with azacitidine for the treatment of *TP53* mutant MDS and/or AML patients in 5 clinical trials, including frontline therapy, relapsed/refractory, or R/R, therapy and post-allo-HCT maintenance therapy. We plan to initiate an additional trial in the second half of 2020 to evaluate APR-246 with venetoclax and rituximab, and APR-246 with ibrutinib in R/R NHL, including CLL and MCL.

The Pivotal Phase 3 MDS Trial

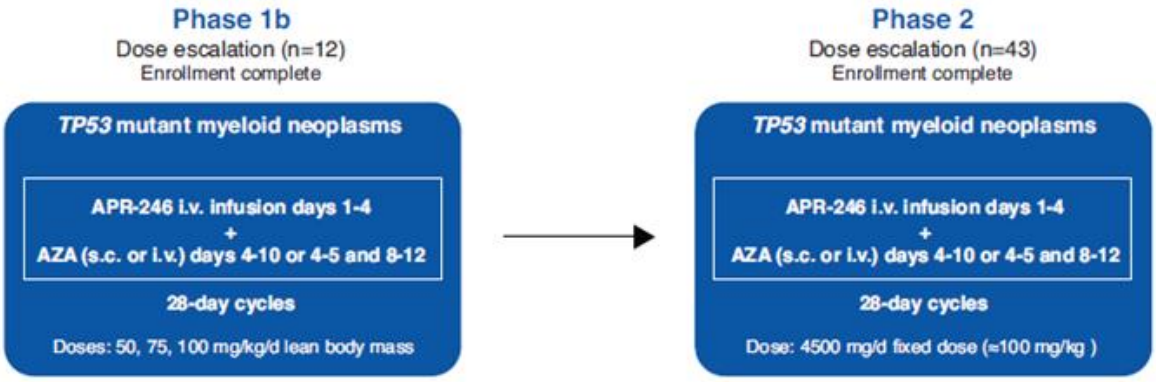
Our pivotal Phase 3 trial commenced enrollment in January 2019. Patients are randomized in a 1:1 ratio to either the azacitidine control arm or to the APR-246 + azacitidine test arm. The primary endpoint is CR rate with secondary endpoints including ORR, duration of response, progression-free survival, or PFS, leukemia-free survival, or LFS, OS, and proportion transitioning to allo-HCT. Serious adverse events, regardless of causality, reported in more than one patient as of March 18, 2020 were: febrile neutropenia (21%), pyrexia (8%), lung infection (7%), muscle weakness (5%), confusional state (3%), pneumonia (3%), respiratory failure (3%), sepsis (3%), cellulitis (2%), acute febrile neutrophilic dermatosis (2%), acute kidney injury (2%), acute respiratory distress syndrome (2%), cardiac failure (2%), dyspnea (2%), encephalopathy (2%), hypotension (2%), hypoxia (2%), pericarditis (2%), thrombocytopenia (2%), pneumonitis (2%), urinary tract infection (2%). There have been two deaths resulting from respiratory failure in patients

receiving both APR-246 and azacitidine and reported by an investigator as possibly related to both study drugs. There has been one death resulting from acute cardiac failure in a patient receiving both APR-246 and azacitidine and reported by an investigator as possibly related to APR-246, and one death resulting from pneumonitis in a patient receiving azacitidine monotherapy and reported by an investigator as possibly related. The target enrollment is 154 patients and we had anticipated completing enrollment in the first quarter of 2020 and top-line CR data in the second half of 2020. We have observed a recent decrease in both patient screening and patient enrollment as a result of the recent coronavirus *(COVID-19)* pandemic. Together with our investigators and clinical sites, we are assessing the potential impact of the coronavirus pandemic and the corresponding impact on enrollment and the ability to maintain patients enrolled in this trial and the corresponding impact on the timing of the completion of the trial and subsequent availability of top-line data.

The U.S. Phase 1b/2 MDS/AML Trial

We are supporting an investigator-initiated Phase 1b/2 single-arm, open-label, multi-center trial in the United States of APR-246 with azacitidine in HMA-naïve patients with *TP53* mutant myeloid neoplasms including MDS and AML. Enrollment commenced in May 2017 and was completed in March 2019. The Phase 1b part enrolled 12 patients and was conducted as a dose escalation in a modified 3+3 design at dose levels of 50 mg/kg/d, 75 mg/kg/d and 100 mg/kg/d, calculated by lean body mass. The Phase 2 part enrolled 43 patients with all patients receiving a fixed dose of 4500 mg/d APR-246, a dose that our population pharmacokinetic analysis has identified as approximately equivalent to the highest Phase 1b dose, 100 mg/kg/d by lean body mass. A lead-in phase, beginning two weeks prior to starting cycle 1 of combination therapy with azacitidine, was conducted only in the Phase 1b part. The purpose of the lead-in phase was to establish the adverse event profile of APR-246 in this patient population and to APR-246-induced p53 reactivation. The protocol specifies administration of APR-246 as a 6-hour intravenous infusion daily for four consecutive days, with administration of 75 mg/m^2/d azacitidine by sub-cutaneous injection or intravenously beginning on Day 4 after completion of APR-246 infusion and continuing for 6 additional days. The image below shows the design of the U.S. Phase 1b/2 MDS/AML Trial.

Design of the U.S. Phase 1b/2 MDS/AML Trial



Baseline characteristics of patients enrolled in the trial are shown in the following table. Patients with MDS, AML, chronic myelomonocytic leukemia, or CMML, and MDS-myeloproliferative neoplasm overlap, or MDS-MPN, were allowed to enroll in the trial. Most patients were higher risk MDS (35/55, 64%) or AML (11/55, 20%), with complex karyotypes, cytopenias and transfusion dependence.

Baseline characteristics

	All patients (n=55)
Female / Male, n	29 / 26
Age in years, median (range)	66 (34 - 85)
Age Category, n (%)	
< 65	23 (42)
≥ 65	32 (58)
ECOG PS(1) at treatment start, n (%)	
0	17 (31)
1	34 (62)
2	4 (7)
Disease type, n (%)	
MDS	40 (73)
IPSS-R(2): Intermediate	4 (7)
IPSS-R: High	8 (15)
IPSS-R: Very High	28 (51)
AML	11 (20)
CMML(3)	2 (4)
MDS-MPN(4)	2 (4)
Therapy-related(5), n (%)	18 (33)
Chemotherapy	16 (29)
Radiation	3 (5)
Complex karyotype, n (%)	47 (85)
***TP53* VAF(6)%, median (range)**	21 (1 - 79)
Bone marrow blast %, median (range)	8 (0 - 30)
Hematology, median (range)	
ANC(7), 10^3/µL	1.19 (0.02 - 15.98)
Hgb(8), g/dL	8.6 (6.7 - 13.8)
Platelets, 10^3/µL	46 (0 - 845)
WBC(9), 10^3/µL	2.4 (0.6 - 30.8)
Transfusion dependence, n (%)	
RBC(10)	36 (65)
Platelets	12 (22)

(1) Eastern Cooperative Oncology Group performance status

(2) Revised International Prognostic Scoring System

(3) Chronic myelomonocytic leukemia

(4) Myelodysplastic syndromes-myeloproliferative neoplasms overlap

(5) Patients treated for prior cancer(s)

(6) Variant allele frequency

(7) Absolute neutrophil count

(8) Hemoglobin

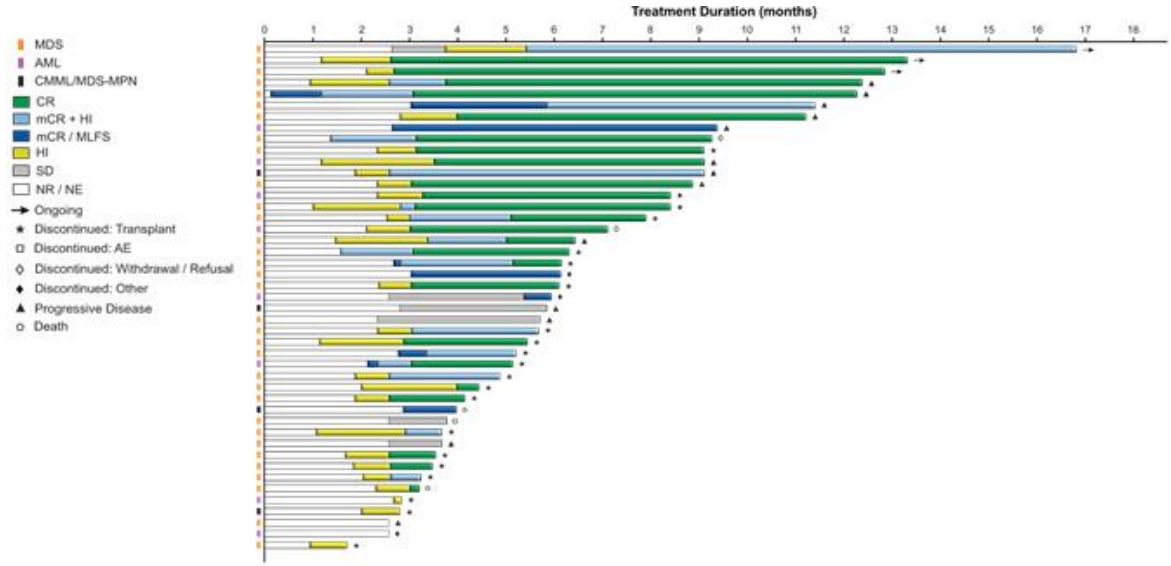
(9) White blood cell

(10) Red blood cell

The median age of all enrolled patients was 66 years, consistent with MDS and AML affecting mostly older patients. Of the MDS patients in the trial, 36/40 were high or very high risk by IPSS-R. Across all patients, 33% had documented therapy-related disease and 85% had complex karyotypes. High risk patients with complex karyotypes and *TP53* mutation have been reported to have the poorest prognosis of all MDS and AML patients. The median bone marrow blast percentage was 8%. Hematologic parameters were reflective of the frequently severe cytopenias attendant with MDS and AML and were underscored by transfusion dependence at baseline in 69% of patients.

Of the 51 MDS and AML patients treated with the combination of APR-246 and azacitidine, 41 had at least one serial bone marrow biopsy performed and were evaluable for response in accordance with trial protocol as of November 15, 2019. In addition, 4 patients with CMML or MDS-MPN were evaluable for response at the same data cutoff. In the subset of 41 evaluable MDS and AML patients, responses were reported in 29/33 (88%) MDS patients and 7/8 (88%) AML patients. In MDS patients, the CR rate was 61%, with an additional 27% achieving non-CR responses. In AML patients, the CR rate was 50%, with an additional 38% achieving non-CR responses. Twenty-one of 41 (51%) MDS/AML patients discontinued treatment for allo-HCT, as transplant is viewed as a potentially curative option for patients with *TP53* mutant MDS and AML. Treatment duration and responses are shown in the figure below. The median time to first response was 1.9 months in MDS patients and 2.2 months in AML patients. With a median follow up of 10.8 months, the median duration of response in evaluable patients was 8.0 months (95% confidence interval: 6.5 – 11.2 months) and the median duration of CR was 7.3 months (95% confidence interval: 5.8 months – not estimable). The median duration of response in MDS patients was 8.4 months (95% confidence interval: 6.5 – 13.2 months) and the median duration of CR was 7.3 months (95% confidence interval: 7.3 months – not estimable) in MDS patients and 7.0 months (95% confidence interval: 3.3 months – not estimable) in AML patients. By intention to treat analysis, median OS was 10.8 months (95% confidence interval: 8.1 − 13.4 months) with significantly prolonged OS of 13.7 months (95% confidence interval: 10.8 – 16.5 months) in responding patients versus 3.9 months (95% confidence interval: 1.9 – 6.0 months) in non-responding patients ($p < 0.0001$).

Treatment duration and response in evaluable patients in the U.S. Trial
Data cutoff: November 15, 2019 (n=45)



Treatment with azacitidine is the standard of care for frontline therapy in *TP53* mutant MDS and AML, with ORR of 40-45% and a CR rate of 15-20%. A limited number of peer-reviewed publications have reported the duration of response, or DoR, in this patient population; from the available public data, DoR is approximately 4-5 months.

Reported adverse events, or AEs, were mostly low-grade (Grade 1 or 2). Grade 3 or higher AEs were mostly associated with the underlying disease. In the APR-246 monotherapy lead-in phase there were no dose-limiting toxicities, no serious adverse events attributed to APR-246 and all treatment-related AEs were low-grade. The following chart summarizes the AEs reported in more than one patient during the APR-246 monotherapy lead-in phase.

AEs reported in > 1 patient during APR-246 monotherapy lead-in phase (n=12)

Adverse event, n (%)	Any grade	Grade ≥ 3
Nausea	5 (42)	0 (0)
Peripheral sensory neuropathy	5 (42)	0 (0)
Back pain	3 (25)	0 (0)
Febrile neutropenia	2 (17)	2 (17)
Anemia	2 (17)	2 (17)
Headache	2 (17)	0 (0)
Dizziness	2 (17)	0 (0)

The most common AEs observed across all cycles of treatment in the trial, as of March 18, 2020 and regardless of causality, are summarized in the following chart. Only three patients (5%) discontinued treatment due to AE. Serious adverse events, regardless of causality, reported for more than one patient were: febrile neutropenia (33%), pneumonia (20%), sepsis (11%), lung infection (9%), pyrexia (7%), dehydration (5%), muscle weakness (5%), respiratory failure (5%), vomiting (5%), angina (4%), atrial fibrillation (4%), embolism (4%), intracranial hemorrhage (4%), multi-organ failure (4%).

Most common reported AEs with APR-246 + azacitidine treatment, regardless of causality (≥20%)
Data cutoff: November 15, 2019 (n=55)

Adverse event, n (%)	Any grade	Grade ≥ 3
Nausea	35 (64)	0 (0)
Vomiting	25 (45)	1 (2)
Fatigue	24 (44)	0 (0)
Constipation	23 (42)	0 (0)
Edema	21 (38)	2 (4)
Dizziness	20 (36)	1 (2)
Diarrhea	18 (33)	1 (2)
Febrile neutropenia	18 (33)	18 (33)
Peripheral sensory neuropathy	17 (31)	0 (0)
Leukopenia	17 (31)	16 (29)
Dyspnea	16 (29)	1 (2)
Headache	16 (29)	0 (0)
Lung infection	16 (29)	14 (25)
Neutropenia	16 (29)	16 (29)
Thrombocytopenia	16 (29)	14 (25)
Cough	15 (27)	1 (2)
Pruritus	14 (25)	0 (0)
Anorexia	13 (24)	0 (0)
Ataxia / unsteady gait	13 (24)	2 (4)
Fever	12 (22)	1 (2)
Alanine aminotransferase increased	11 (20)	1 (2)
Mucositis oral	11 (20)	0 (0)
Tremor	11 (20)	1 (2)

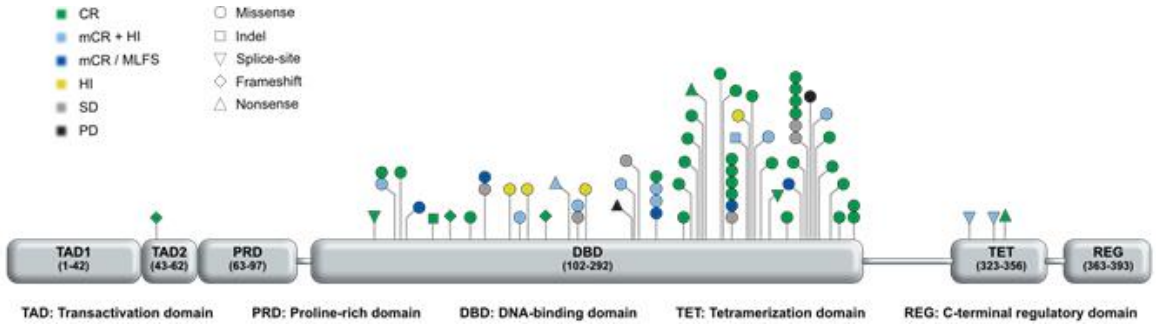
The most common AEs, determined by an investigator to be possibly, probably or definitely related to APR-246 or azacitidine, are summarized in the following chart.

Most common reported AEs with possible, probable or definite relation to APR-246 or azacitidine (≥10%) Data cutoff: November 15, 2019 (n=55)

Adverse event, n (%)	Any grade	Grade ≥ 3
Nausea	31 (56)	0 (0)
Vomiting	25 (45)	1 (2)
Dizziness	16 (29)	1 (2)
Constipation	14 (25)	0 (0)
Leukopenia	13 (24)	12 (22)
Peripheral sensory neuropathy	12 (22)	0 (0)
Thrombocytopenia	11 (20)	9 (16)
Neutropenia	10 (18)	10 (18)
Ataxia / unsteady gain	8 (15)	2 (4)
Tremor	8 (15)	0 (0)
Fatigue	8 (15)	0 (0)
Pruritus	7 (13)	0 (0)
Anorexia	7 (13)	0 (0)

Sixty-six *TP53* mutations, representing 49 unique mutations, were identified in the subset of 45 evaluable patients. Consistent with prior published findings, the majority of these were missense mutations (80%) and located in the DNA-binding domain (94%). Other *TP53* mutations sequenced in the 45 evaluable patients included insertion-deletion mutations (3%), splice-site mutations (6%), frameshift mutations (5%) and nonsense mutations (6%). Patients with a *TP53* mutation alone predicted for CR (69% vs 25%, P=0.0062) with a trend for higher ORR (93% vs 69%, P=0.08). The distribution of *TP53* mutations by type and breadth of mutations by response are shown in the figure below.

***TP53* mutations by type and best response in evaluable patients**
Data cutoff: November 15, 2019 (n=45)



The French Phase 1b/2 MDS/AML Trial

We are supporting an ongoing investigator-initiated single-arm, open-label Phase 1b/2 trial in France by the Groupe Francophone des Myélodysplasies, or GFM, under lead investigator Prof. Pierre Fenaux, to expand the adverse event and efficacy data set in MDS and AML patients treated with the combination of APR-246 and azacitidine. The trial was initiated in September 2018 and reached final enrollment of 53 patients in July 2019. The median age of enrolled patients is 73 years. 34 of 53 patients (64%) had a diagnosis of MDS and 19 of 53 patients (36%) had a diagnosis of AML. At baseline, 82% of MDS patients were very high risk by IPSS-R. Complex karyotype was found in 87% of enrolled patients.

The protocol specifies daily administration of 4500 mg/d APR-246 as a 6-hour intravenous infusion daily for four consecutive days, with administration of 75 mg/m^2/d azacitidine by sub-cutaneous injection or intravenously beginning on Day 4 after completion of APR-246 infusion and continuing for 6 additional days. Treatment cycles are 28 days in duration. Patients who receive benefit from frontline therapy and undergo allo-HCT are eligible to continue with

post-transplant maintenance therapy with APR-246 and azacitidine. Data were reported in December 2019 for 38 patients evaluable for response in accordance with trial protocol, including 27 MDS patients and 11 AML patients. Responses were achieved in 20/27 (74%) MDS patients with 59% CR rate, and 6/11 (55%) AML patients with a 44% CR rate in AML patients having 20-30% bone marrow blasts, for a combined 68% ORR and 53% CR rate.

Serious adverse events, regardless of causality, reported in more than one patient in the French Phase 1b/2 MDS/AML Trial as of March 18, 2020 were: Febrile neutropenia (30%), device related infection (9%), sepsis (8%), lung disorder (6%), ataxia (4%), cellulitis (4%), colitis (4%), dizziness (4%), large intestine infection (4%), lung infection (4%), pneumonia (4%), septic shock (4%), subdural hematoma (4%), urinary tract infection (4%). There have been three deaths reported by an investigator as possibly related to azacitidine: one resulting from respiratory failure, one resulting from lung disorder, and one resulting from gastrointestinal hemorrhage and septic shock.

The Phase 2 MDS/AML Post-transplant Trial

There is a significant unmet medical need for more effective therapies for patients with *TP53* mutant AML and MDS following allo-HCT given that the one-year post-transplant relapse-free survival, or RFS, rate is only 30%. In the second quarter of 2019, we opened enrollment to our Phase 2 MDS/AML Post-Transplant Trial to evaluate the benefit of APR-246 with azacitidine on RFS in *TP53* mutant MDS and AML patients who have received allo-HCT. The protocol specifies administration of 3700 mg/d APR-246 as a 6-hour intravenous infusion daily on days 1 through 4, with administration of 35 $mg/m^2/d$ azacitidine by sub-cutaneous injection or intravenously on days 1 through 5. Patients may receive a maximum of 12 cycles of maintenance therapy in the Phase 2 MDS/AML Post-Transplant Trial. As of March 18, 2020, there have been no serious adverse events, regardless of causality, reported in more than one patient. Target enrollment in the trial is 31 patients and the primary endpoint is 1-year RFS. In addition, we will evaluate the adverse event profile of APR-246 with azacitidine as maintenance treatment post-HCT. Together with our investigators and clinical sites, we are assessing the potential impact of the coronavirus pandemic on enrollment and the ability to maintain patients enrolled in this trial.

The Phase 1 AML Trial

We are conducting a Phase 1 clinical trial evaluating the adverse event profile and efficacy of treatment with APR-246 and ABT-199/venetoclax, the Bcl-2 inhibitor, with or without azacitidine, in frontline and R/R *TP53* mutant AML. Bcl-2 is a pro-survival protein that is frequently expressed at high levels in tumor cells and acts to restrict apoptosis. Inhibition of Bcl-2 protein relieves its anti-apoptotic function, thereby augmenting apoptosis. In preclinical studies, we have observed strong synergy when APR-246 and the Bcl-2 inhibitor are combined in the *TP53* mutant AML cell line, KBM3 and believe that this combination may provide meaningful improvements in durable responses for *TP53* mutant AML patients with previously untreated and relapsed/refractory AML.

Under the trial design, frontline and R/R *TP53* mutant AML patients who have received prior HMA therapy will receive treatment with APR-246 and venetoclax, and frontline patients who are HMA-naïve will receive treatment with APR-246, venetoclax and azacitidine. We intend to expand the number of patients in individual arms of the trial in a Phase 2 part, as warranted by adverse event and efficacy data, to enable a path to registration in frontline and R/R AML. Together with our investigators and clinical sites, we are assessing the potential impact of the coronavirus pandemic on enrollment and the ability to maintain patients enrolled in this trial.

Serious adverse events, regardless of causality, reported in more than one patient in the Phase 1b/2 AML Trial as of March 18, 2020 were: febrile neutropenia (50%), sepsis (25%).

The Phase 1 NHL Trial

We have designed and plan to conduct a Phase 1 clinical trial evaluating the adverse event profile and efficacy of APR-246 with venetoclax and rituximab, and APR-246 with ibrutinib in R/R *TP53* mutant CLL and MCL. We intend to expand the number of patients in individual arms of the trial in a Phase 2 part, as warranted by adverse event and efficacy data. We are targeting enrollment of the first patient in the second half of 2020.

Clinical development in solid tumors

Phase 1/2 Clinical Trial of APR-246 in R/R Gastric, Bladder and Non-Small Cell Lung Cancers

We have designed and plan to conduct a Phase 1/2 clinical trial evaluating the adverse event profile and preliminary efficacy of APR-246 with anti-PD-1 therapy in R/R gastric cancer, bladder cancer and non-small cell lung cancer. In preclinical studies reported by Ghosh and colleagues from Memorial Sloan Kettering Cancer Center at the 2019 AACR annual meeting, we have observed synergy in mouse cancer models when APR-246 was combined with immuno-oncology agents, including anti-PD-1. The trial will enroll both *TP53* mutant and *TP53* wild-type patients, and we are targeting enrollment of the first patient in the second half of 2020.

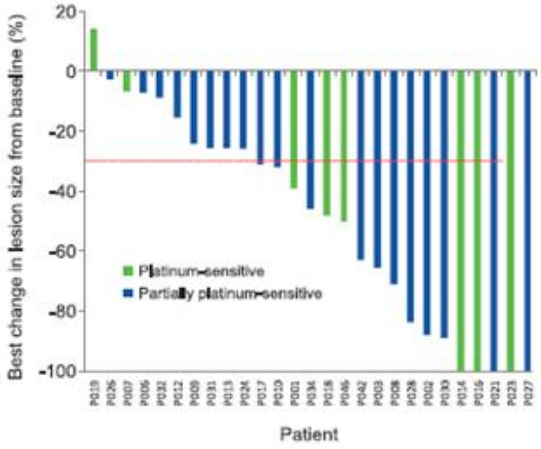
Phase 1b/2 Clinical Trial of APR-246 in Platinum-Sensitive Ovarian Cancer, or PiSARRO

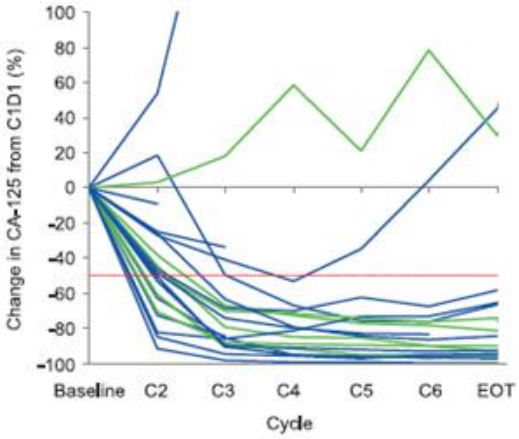
As part of the early development strategy, APR-246 was evaluated in clinical trials in ovarian cancer and this decision was based on the anticipated market size and high prevalence of *TP53* mutation of greater than 95% in high-grade serous ovarian cancer, or HGSOC. In March 2014, a Phase 1b trial was initiated as a part of a combined Phase 1b/2 protocol in platinum-sensitive HGSOC to evaluate APR-246 with carboplatin and pegylated liposomal doxorubicin, or PLD. All patients had previously been treated with platinum-based antineoplastic agents and all had accumulation of p53, as assessed by immunohistochemistry, or IHC, as a surrogate marker of mutant p53. Archival samples were available for 29 patients, of which 27 had DNA of sufficient quality for sequencing and all 27 were confirmed to be *TP53* mutant.

The completed Phase 1b part of the trial was conducted as a dose-escalation in 35 platinum-sensitive and partially platinum-sensitive patients. The primary trial objectives of the Phase 1b portion were to assess the adverse event profile of APR-246 with carboplatin and PLD, to determine a recommended Phase 2 dose level, or RP2D, and to evaluate the pharmacokinetics of APR-246 with carboplatin and PLD. Tumor response was a secondary objective.

The most frequently reported APR-246-related AEs were nausea, dizziness and fatigue, of which most were low-grade. A limited number of APR-246-related grade 3+ AEs were reported, including neutropenia (37%), vomiting (14%), thrombocytopenia (9%), dizziness (6%), anemia (6%), fatigue (3%), headache (3%) and decreased appetite (3%). Serious adverse events, regardless of causality, reported in more than one patient were: device related infection (17%), vomiting (17%), febrile neutropenia (8%), infection (6%), small intestinal obstruction (6%) and thrombocytopenia (6%).

Although efficacy was not a Phase 1b trial objective, tumor response was evaluated. A 67% ORR was observed in 27 patients who were evaluable for radiological response according to RECIST 1.1, including 11% with complete response and 56% with partial response. In addition, an 84% ORR was observed in 25 patients who were evaluable for CA-125 response according to Gynecologic Cancer InterGroup, or GCIG, criteria. Reductions in lesion size and declines in CA-125 are shown in the following figure below. All patients who were evaluable by RECIST 1.1 achieved a best response of stable disease or better, where stable disease indicates lack of objective response but without disease progression. The median time between prior platinum therapy and disease progression prior to enrollment in the trial, known as platinum free interval, or PFI, was 9.4 months, and 40% of patients had received more than one prior line of platinum-based chemotherapy. Two-thirds of patients enrolled in the trial were partially platinum-sensitive, with PFI 6-12 months. The remaining one-third of patients were platinum-sensitive, with PFI greater than 12 months. The median progression-free survival, or PFS, was 10.2 months across all patients and was 10 months and 11.4 months in partially platinum-sensitive and platinum sensitive patients, respectively. The median OS was 24.3 months. This was the first clinical trial of APR-246 with cytotoxic chemotherapy and we believe that the data demonstrated that the agent can be combined with carboplatin and PLD at standard doses.





Data supporting the carboplatin and PLD doublet as a treatment option in platinum-sensitive HGSOC were generated in the CALYPSO trial, a phase 3 clinical trial sponsored by an international consortium of 10 cancer research organizations. The CALYPSO trial enrolled 976 patients, randomized to receive either carboplatin and PLD (48%) or carboplatin and paclitaxel (52%). All patients had received a maximum of two prior lines of chemotherapy; in the carboplatin and PLD arm, 88% had received one prior line and 12% had received two prior lines. The median interval since last chemotherapy, or therapy-free interval, was 15.2 months in the carboplatin and PLD arm, of whom 35% had a therapy-free interval of 6-12 months and 65% had a therapy-free interval in excess of 12 months. The most frequently reported AEs in the carboplatin and PLD arm included neutropenia (80%), nausea (78%), fatigue (78%), anemia (66%), constipation (55%) and vomiting (49%). The most common grade 3+ AEs included neutropenia (35%), thrombocytopenia (16%) and anemia (8%). In the carboplatin and PLD arm PFS was reported as 11.3 months and OS as 30.7 months. Median PFS in the carboplatin and PLD arm was greater than the 9.4 months PFS in the carboplatin and paclitaxel arm (hazard ratio: 0.821, 95% CO, 0.72 – 0.94, P = 0.005). Response rates were not reported for the CALYPSO trial. Whereas the CALYPSO trial enrolled a majority of patients with treatment-free interval exceeding 12 months, our PiSARRO Phase 1b trial enrolled a majority of patients with partially platinum-sensitive disease which is generally recognized as a patient population with inferior treatment outcomes.

In the third quarter of 2016, enrollment commenced in the Phase 2 portion of the PiSARRO trial and concluded at 211 patients. The Phase 2 part was an open-label, randomized, controlled multi-center trial to assess whether patients with platinum-sensitive recurrent HGSOC would benefit from treatment with APR-246 in combination with carboplatin/PLD chemotherapy regimen. All patients were required to have accumulation of p53 as assessed by immunohistochemistry, a surrogate marker of mutant p53.

Patients were randomized in a 1:1 ratio to receive either APR-246 with carboplatin and PLD or carboplatin and PLD only, with treatment to be repeated every 28 days for up to six cycles. Enrollment was concluded in April 2018. The primary endpoint for the Phase 2 part is PFS, defined as the time from registration to the time of disease progression or relapse or death, or the date of last tumor assessment without any such event. Serious adverse events, regardless of causality, reported in more than one patient were: small intestine obstruction (4%), thrombocytopenia (2%), dyspnea (2%), nausea (2%), renal impairment (2%), vomiting (2%), abdominal pain, (1%) anemia (1%), constipation (1%), dehydration (1%), dizziness (1%), infectious pleural effusion (1%), large intestine perforation (1%), urinary tract infection (1%). Upon receipt of final data, we intend to conduct a subset analysis of clinical and molecular characteristics that may influence response and PFS in these patients and anticipate completing this analysis in 2020.

Phase 2 clinical trial of APR-246 in platinum-resistant ovarian cancer, or PiSARRO-R

In July 2017 we initiated an open-label, multicenter Phase 2 trial, PiSARRO-R, to evaluate the adverse event profile and preliminary efficacy of varying infusion regimens of APR-246 with systemic PLD chemotherapy in platinum-resistant HGSOC. The trial enrolled 36 patients and all patients were required to have recurrent disease with PFI between 4 weeks

and 6 months, and accumulation of p53 as assessed by immunohistochemistry, a surrogate marker of mutant p53. The majority (69%) of patients had received 2 or more prior lines of chemotherapy. Patients received either a 4500 mg/d fixed dose of APR-246 as a 6 hour intravenous infusion (n=28, 78%), or the same or lower fixed dose over 3 or 4 hours (n=8, 22%) for four consecutive days, followed by 40 mg/m^2 PLD on Day 4. The most frequently reported APR-246-related AEs were nausea, vomiting and dizziness. Limited APR-246-related grade 3+ AEs were reported, of which only anemia (n=3, 8%) was observed in more than one patient. Serious adverse events, regardless of causality, reported in more than one patient were: Intestinal obstruction (n=3, 8%) and infection (n=2, 6%). We believe the available adverse event data from the trial demonstrates that reduced duration infusion regimens with APR-246 are feasible.

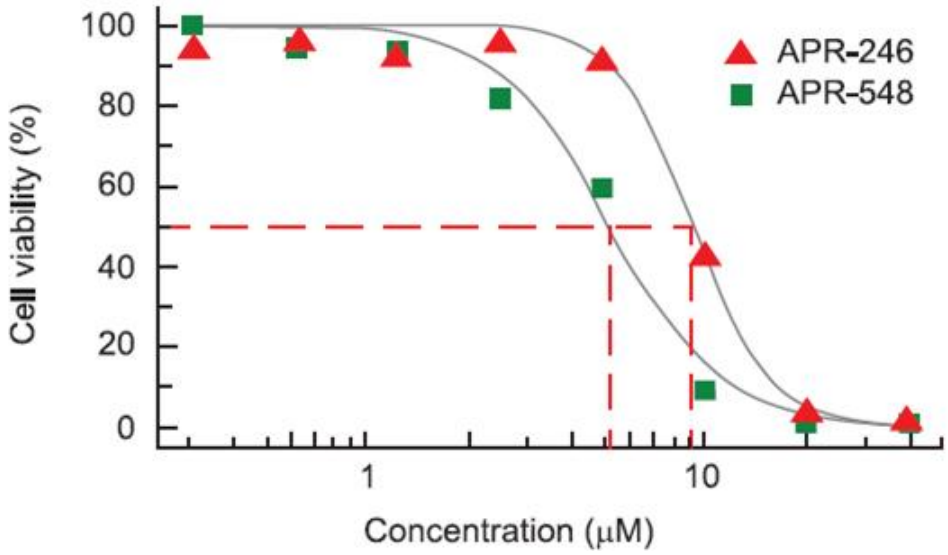
As part of the PiSARRO trials, we are collaborating with the European Network for Translational Research in Ovarian Cancer, or EUTROC, with the aim to identify predictive markers of efficacy, tolerability and clinical pharmacology.

Our second product candidate, APR-548

We are developing a next-generation small molecule mutant p53 reactivator, APR-548, a novel pro-drug of MQ that has the potential to be administered in an oral dosage form. We intend to initially develop APR-548 in *TP53* mutant hematological malignancies. We believe that an oral p53-reactivating drug will improve patient convenience and compliance, if approved, including for patients receiving prolonged therapy in the maintenance setting.

In preclinical testing we have observed potency with APR-548 that was superior to that of APR-246 in a Saos-2 osteosarcoma cell line expressing an Arg273His mutant p53 and the MIA-PaCa-2 pancreatic cancer cell line harboring an Arg248Trp mutant p53. The half maximal inhibitory concentration, or IC_{50}, in the Saos-2 cell line was calculated to be 5.6 µM ± 1.0 µM (n=3) for APR-548 and 9.5 µM ± 1.2 µM (n=37) for APR-246, representing an approximately 40% reduction in IC_{50} with APR-548. In the MIA-PaCa-2 cell line, the IC_{50} for APR-548 was calculated to be 6.0 µM (n=1) versus 19 µM (n=1) for APR-246, representing a nearly 70% reduction in IC_{50} with APR-548.

Reduced *in vitro* IC_{50}[(1)] of APR-548 in a p53 mutant saos-2 cell line

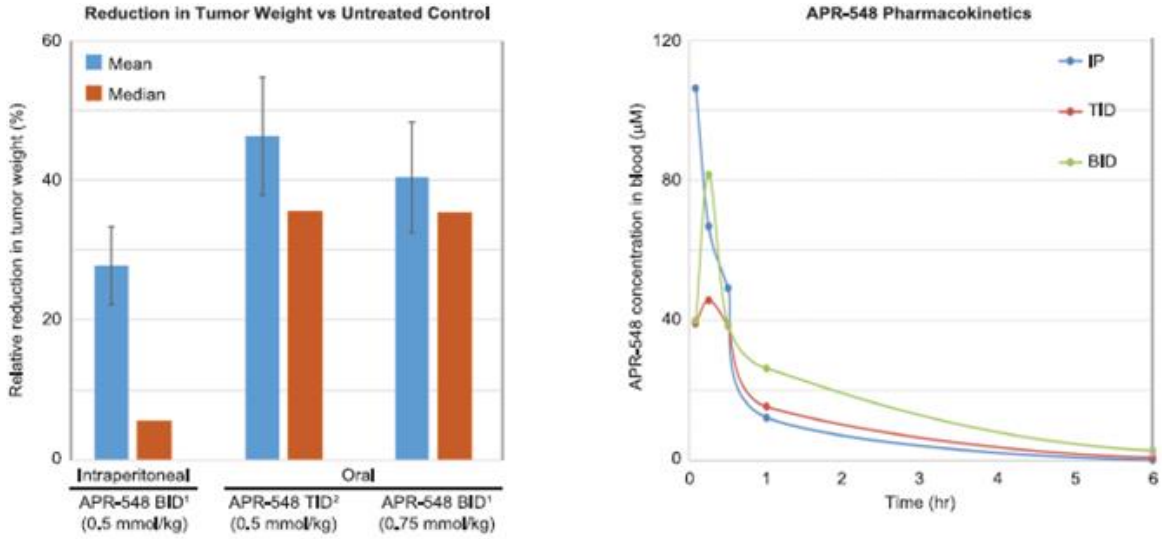


(1) Half-maximal inhibitory concentration

In xenograft studies in which mice were implanted with a breast adenocarcinoma cell line, MDA-MB-231-*luc*, we tested the *in vivo* efficacy of APR-548 when administered by twice-daily intraperitoneal (i.p.) injection, or by twice-daily or three times daily oral (PO) gavage. In these studies, mice received APR-548 for three cycles where each cycle consisted of 5 consecutive days of dosing followed by 2 days without dosing. Tumor growth inhibition was measured on day 33 post-inoculation, 3 days after the final dosing in the final cycle. In mice receiving APR-548 via oral administration, we observed reductions in tumor weight relative to untreated control mice. Results from these studies are summarized in the following table.

Xenograft Study	No. of mice	APR-548/dose (mmol/kg)	Doses/day	Dosing interval (hours)	Route	Tumor growth inhibition (%)
#1	8	0.18	2	8	i.p.	20 ± 2
	8	0.50	2	8	i.p.	26 ± 2
#2	8	0.25	2	8	i.p.	15 ± 2
	8	0.50	3	4	PO	24 ± 2
	8	0.75	2	8	PO	36 ± 5
#3	8	0.50	2	8	i.p.	28 ± 6
	8	0.50	3	4	PO	46 ± 8
	8	0.75	2	8	PO	40 ± 8
	8	0.75	2	1.50	PO	28 ± 5
#4	8	0.19	2	8	PO	3 ± 0.4
	8	0.38	2	8	PO	19 ± 3
	8	0.75	2	8	PO	40 ± 6
	8	1.50	1	—	PO	32 ± 4

In xenograft study #3 we assessed APR-548 pharmacokinetics and confirmed that circulating blood concentrations of APR-548 exceeded levels expected to be efficacious, as determined from *in vitro* results. Results from this xenograft study are summarized graphically in the following figure.



(1) Twice daily

(2) Three times daily

In *in vivo* studies in mouse and dog, we observed high oral bioavailability of APR-548 when dosed as either an aqueous solution or as a solid in capsules. Observed oral bioavailability ranged from 75% to greater than 99%, and with no significant effect of feeding on absorption. Results from these studies are summarized in the following table.

Species	No. of animals	APR-548 dose (mg/kg)	Route	Bioavailability (%)
Mouse (C57Bl/6N)	18	20	PO (solution)	80
Mouse (CD-1)	9	50	PO (solid in capsule)	97
Mouse (CD-1)	9	50	PO (solution)	99
Dog, fed	3	10	PO (solid in capsule)	84
Dog, fasted	3	10	PO (solid in capsule)	83
Dog, fed	3	10	PO (solution)	80
Dog, fasted	3	10	PO (solution)	75

Based on results obtained through our preclinical *in vitro* and *in vivo* studies, we have initiated a series of studies required for IND submission. In our *in vitro* studies, APR-548 has not demonstrated inhibition or induction or metabolic enzymes at concentrations up to 300 μM. Studies testing APR-548 as an inhibitor or substrate of protein transporters have shown weak inhibition, with IC_{50} > 150 μM, is limited to the OCT2 transporter. Additional studies have shown no significant effects when tested at 10 μM in a screen of 87 different receptors, transporters and enzymes, and no effect on the human *ether-a-go-go* channel, or hERG, in a manual patch clamp assay at concentrations up to 100 μM. Metabolic studies have shown that APR-548 is metabolized slowly and all metabolites produced in human cells are also produced in our mouse and dog toxicology species. Pivotal repeat-dose and dose escalation GLP toxicology studies in multiple toxicology species have been completed and final reports are pending.

We have developed a scalable, high-purity process for the manufacture of APR-548 and have completed physical characterization studies to survey the landscape of APR-548 polymorphs with properties favorable for the development of an oral formulation to be used in clinical trials.

Manufacturing

We currently contract with third parties for the manufacture of our product candidates for certain preclinical trials and clinical trial materials, including raw materials and consumables necessary for their manufacture, consistent with applicable cGMP requirements. We have assessed both capacity and the current clinical supply chain associated with the production of APR-246 and are not currently aware of any disruption to our ability to provide supply for our on-going clinical trials. We will continue to monitor and assess the potential impact of the coronavirus pandemic on our clinical trial supply chain. We intend to continue to contract for these materials in the future, including commercial manufacture if our product candidates receive marketing approval. We do not own or operate cGMP manufacturing facilities, nor do we currently plan to build our own cGMP manufacturing capabilities for the production of our product candidates for clinical or commercial use. Although we rely upon contract manufacturers for the manufacture of our product candidates for IND-enabling trials and clinical trials, we have personnel with extensive manufacturing experience who oversee our contract manufacturers. In the future, we may also rely upon collaboration partners, in addition to contract manufacturers, for the manufacture of our product candidates or any products for which we obtain marketing approval.

The active pharmaceutical ingredient, or API, for APR-246 is currently manufactured by a single contract manufacturer. Although we may do so in the future, we do not currently have arrangements in place for redundant supply of the API for APR-246. We contract with a different manufacturer for formulation of drug product, sterile fill of vials, labeling and packaging, and the storage and distribution of APR-246 to clinical sites. We believe that these third parties have sufficient capacity to meet our current demand and, in the event they fail to meet our demand, we believe that adequate alternative sources for the supply of materials for APR-246 exist. We intend to identify and qualify additional manufacturers to provide the API and other services for APR-246 prior to seeking marketing approval for APR-246.

We believe that, because APR-246 is a small molecule, it can be manufactured through reliable and reproducible synthetic processes from readily available raw materials and then purified and packaged for clinical use. We believe that the chemistry process is amenable to scale-up and requires only customary equipment in the manufacturing process.

We have a manufacturing and supply agreement and quality agreement with Syngene International Private Limited for the manufacture of API. We have a service agreement with Cobra Biopharma for the clinical manufacture, labeling and packaging of formulated drug product. We have a manufacturing and supply agreements and quality agreement with Siegfried Hameln GmbH for the commercial manufacture, supply, labeling and packaging of formulated drug product.

Manufacturing clinical products is subject to extensive regulations that impose various procedural and documentation requirements, which govern record keeping, manufacturing processes and controls, personnel, quality control and quality assurance. Our contract manufacturers are required to comply with current good manufacturing practice regulations, which are regulatory requirements for the production of pharmaceuticals that will be used in humans.

Competition

The pharmaceutical and biotechnology industries generally, and the cancer drug sector specifically, are highly competitive and characterized by rapidly advancing technologies, evolving understanding of disease etiology and a strong emphasis on proprietary drugs. While we believe that our product candidates, development capabilities, experience and scientific knowledge provide us with competitive advantages, we face significant potential competition from many different sources, including major pharmaceutical, specialty pharmaceutical and biotechnology companies, academic institutions, governmental agencies and public and private research institutions. Any product candidates that we successfully develop and commercialize will compete with existing therapies and new therapies that may become available in the future.

There are a large number of companies developing or marketing treatments for cancer, including the indications for which we may develop product candidates. Many of the companies that we compete against or may compete against in the future have significantly greater financial resources and expertise in research and development, manufacturing, preclinical testing, conducting clinical trials, obtaining regulatory approvals and marketing approved drugs than we do. Small or early-stage companies may also prove to be significant competitors, particularly through collaborative arrangements with large and established companies. These competitors also compete with us in recruiting and retaining qualified scientific and management personnel and establishing clinical trial sites and patient registration for clinical trials, as well as in acquiring technologies complementary to, or that may be necessary for, our programs.

Our commercial opportunity could be reduced or eliminated if our competitors develop and commercialize drugs that are safer, more effective, have fewer or less severe side effects, are more convenient or are less expensive than any drugs that we may develop. Our competitors also may obtain FDA or other regulatory approval for their drugs more rapidly than we may obtain approval for ours, which could result in our competitors establishing a strong market position before we are able to enter the market. The key competitive factors affecting the success of all of our product candidates, if approved, are likely to be their efficacy, safety, convenience and price, in guiding the use of related therapeutics, the level of generic competition and the availability of reimbursement from government and other third-party payors.

The most common methods of treating patients with cancer are surgery, radiation and therapy with drugs or biologics. There are a variety of available drug therapies marketed for cancer. In many cases, these drugs are administered in combination to enhance efficacy. Some of the currently-approved drug therapies are branded and subject to patent protection and may be established as standard of care for the treatment of indications for which we may choose to seek regulatory approvals. Many of these approved drugs are well-established therapies and are widely accepted by physicians, patients and third-party payors, and even if our drug candidates were to be approved, there can be no assurance that our drugs would displace existing treatments.

In addition to currently marketed therapies, there are also a number of drugs in late-stage clinical development to treat cancer, including for the treatment of the indications for which we are developing product candidates. These clinical-stage drug candidates may provide efficacy, safety, convenience and other benefits that are not provided by currently-marketed therapies. As a result, they may provide significant competition for any of our product candidates for which we obtain regulatory approval.

We are developing our lead product candidate, APR-246, to reactivate p53 for the treatment of various cancers. We are aware of other product candidates that are in clinical development as potential treatments of various cancers through the

reactivation of p53. Although there is a subset of drugs that directly target the p53 pathway, there are many cancer drugs that claim to affect the p53 pathway by upstream or complementary pathways. We are aware of molecules in development that also are being explored for p53 upregulation / activation in various stages of clinical development being tested by CDG Therapeutics, Inc., Innovation Pharmaceuticals, Inc., MedVax Technologies, Inc., PMV Pharmaceuticals, Inc., and Senhwa Biosciences, Inc., among others. We are also aware of selective small molecule inhibitors that are designed to target the p53-MDM2 interaction in various stages of clinical development being tested by F-Hoffman La Roche Ltd and Hoffman La Roche Inc., or collectively Roche, Amgen Inc., Novartis AG, Aileron Therapeutics and Daiichi Sankyo Co., Ltd., including testing MDM2 inhibitors in combination with a variety of other anti-cancer agents. Finally, we are aware of several small molecules that are designed to inhibit the activity of Bcl-2 and the related protein Mcl-1 and relieve inhibition of the apoptotic cascade. Abbvie Inc.'s venetoclax has been approved in AML and chronic lymphocytic leukemia; companies with Bcl-2 or Mcl-1 inhibitors in various stages of preclinical or clinical development include Amgen Inc., Servier SAS, AstraZeneca Plc and Pfizer Inc., among others.

If APR-246 was approved for the indications for which we currently have ongoing clinical trials, it will compete with currently-marketed drugs and will likely compete with other drugs that are currently in clinical development, each as discussed below.

MDS / AML

The front-line treatments for patients with higher-risk MDS in the United States are combination chemotherapy or HMAs such as Dacogen (decitabine) or Vidaza (azacitidine). We are aware of several ongoing clinical trials aimed at expanding the use of approved chemotherapy and immunomodulatory agents in higher-risk MDS, as well as several new clinical programs testing novel technologies in this area, including product candidates from Abbvie Inc., argenx, Astex Pharmaceuticals, Inc., Celgene Corporation, CTI BioPharma Corp., Cyclacel Pharmaceuticals, Inc., Eisai Co., Ltd., Forty Seven Inc., Karyopharm Therapeutics Inc., Onconova Therapeutics, Inc., and Takeda Pharmaceutical Company Limited.

CLL

Due to poor responses to traditional chemotherapy agents, CLL patients in the United States with high-risk 17p deletion and/or p53 mutation are typically treated with BCR inhibitors such as ibrutinib, Bcl-2 inhibitors such as venetoclax, and anti-CD20 antibodies such as rituximab. We are aware of several ongoing clinical trials aimed at expanding the use of approved targeted chemotherapy and immunomodulatory agents in high-risk CLL, as well as several new clinical programs testing novel technologies in this area, including product candidates from AbbVie Inc., AstraZeneca Plc, Bayer AG, BeiGene Ltd, Bristol-Myers Squibb Co, F. Hoffman-La Roche Ltd, Gilead Sciences Inc., Incyte Corp, Johnson & Johnson, Juno Therapeutics Inc., Karyopharm Therapeutics Inc., Merck & Co Inc., Novartis AG, Ono Pharmaceutical Co Ltd., Takeda Pharmaceutical Co Ltd, and TG Therapeutics Inc.

MCL

The preferred treatment option for R/R MCL patients in the United States is a BTK inhibitor such as ibrutinib or acalabrutinib. We are aware of several ongoing clinical trials aimed at expanding the use of approved chemotherapy and immunomodulatory agents in MCL, as well as several new clinical programs testing novel technologies in this area, including product candidates from AbbVie Inc., Amgen Inc, AstraZeneca Plc, Bayer AG, BeiGene Ltd, Bristol-Myers Squibb Co, F. Hoffman-La Roche Ltd, Gilead Sciences Inc., Incyte Corp, Johnson & Johnson, Juno Therapeutics Inc., Karyopharm Therapeutics Inc., Merck & Co Inc., and TG Therapeutics Inc.

Gastric cancer

The preferred treatment options for R/R gastric cancer in the United States are dependent on regimens received in first-line therapy as well as patient performance status. Second- and later-line treatments include taxanes, fluoropyrimidines, ramucirumab, irinotecan and pembrolizumab. We are aware of several ongoing clinical trials aimed at expanding the use of approved chemotherapy and immunomodulatory agents in R/R gastric cancer, as well as several new clinical

programs testing novel technologies in this area, including product candidates from Altor Bioscience LLC, BeiGene Ltd, Bristol-Myers Squibb Co,, Incyte Corp, Merck & Co Inc., Pfizer Inc., and TG Therapeutics Inc.

Bladder cancer

The preferred treatment option for R/R bladder cancer in the United States is the anti-PD-1 antibody, pembrolizumab, Alternative regimens include other anti-PD-1 antibodies, antibodies targeting PD-L1 or CD274, FGFR inhibitors, taxanes, and topoisomerase inhibitors. We are aware of several ongoing clinical trials aimed at expanding the use of approved chemotherapy and immunomodulatory agents in R/R bladder cancer, as well as several new clinical programs testing novel technologies in this area, including product candidates from Altor Bioscience LLC, AstraZeneca Plc,, Bristol-Myers Squibb Co,, F. Hoffman-La Roche Ltd, and Merck & Co Inc.

NSCLC

The preferred treatment options for R/R NSCLC depend on tumor subtype and the presence of tumor biomarkers such as genetic mutations or PD-L1 expression. Therapeutic agents include pembrolizumab, nivolumab, ipilimumab, platinum agents, taxanes, and topoisomerase inhibitors. We are aware of several ongoing clinical trials aimed at expanding the use of approved chemotherapy and immunomodulatory agents in R/R NSCLC, as well as several new clinical programs testing novel technologies in this area, including product candidates from AbbVie Inc,, AstraZeneca Plc., Bayer AG, Bristol-Myers Squibb Co,, F. Hoffman-La Roche Ltd, Gilead Sciences Inc., Karyopharm Therapeutics Inc., Milennium Pharmaceuticals Inc. and Pfizer Inc.

Intellectual property

We strive to protect the proprietary technologies that we believe are important to our business, including seeking and maintaining patent protection intended to cover the methods-of-use, formulations, dosing, manufacturing processes, and crystalline solid form of one or more of our product candidates, including APR-246, and composition of matter of our other product candidates, related technology, and other inventions that are important to our business.

Our success will depend significantly on our ability to obtain and maintain patent and other proprietary protection for commercially important technology, inventions, and know-how related to our business, defend and enforce our patents, preserve the confidentiality of our trade secrets, and operate without infringing the valid and enforceable patents and other proprietary rights of third parties.

A third party may hold intellectual property, including patent rights, which are important or necessary to the development or commercialization of our product candidates. If it becomes necessary for us to use patented or proprietary technology of third parties to develop or commercialize our product candidates, we may need to seek a license from such third parties. Our business could be harmed, possibly materially, if we are unable to obtain such a license on terms that are commercially reasonable, or at all.

We may seek to expand our intellectual property estate by filing patent applications directed to dosage forms, methods of treatment, diagnostics, and additional compounds and their derivatives. Specifically, we have sought and will continue to seek patent protection in the United States and internationally for novel compositions of matter covering the compounds of our product candidates other than APR-246 and a crystal form of APR-246, the chemistries and processes for manufacturing these compounds, and the use of these compounds in a variety of therapies. The chemical structure of APR-246 is in the public domain. Accordingly, we do not own or license any composition of matter patents claiming the compound of APR-246 and will not in the future own or license any composition of matter patents claiming the chemical structure of APR-246 as described in the public domain.

The patent positions of biopharmaceutical companies like us are generally uncertain and involve complex legal, scientific and factual questions. In addition, the coverage claimed in a patent application can be significantly reduced before the patent is issued, and its scope can be reinterpreted after issuance. Consequently, we do not know whether any of our product candidates will be protectable or remain protected by enforceable patents. We cannot predict whether the patent applications we are currently pursuing will issue as patents in any particular jurisdiction or whether the claims of

any issued patents will provide sufficient proprietary protection from competitors. Any patents that we hold may be challenged, circumvented or invalidated by third parties.

Because patent applications in the United States and certain other jurisdictions are maintained in secrecy for 18 months, and since publication of discoveries in the scientific or patent literature often lags actual discoveries, we cannot be certain of the priority of inventions covered by pending patent applications. Moreover, we may have to participate in interference proceedings declared by the United States Patent and Trademark Office, or USPTO, to determine priority of invention or in post-grant challenge proceedings at the USPTO or at a foreign patent office, such as inter partes review and post grant review proceedings at the USPTO and opposition proceedings at the European Patent Office, that challenge priority of invention or other features of patentability. Such proceedings could result in substantial cost, even if the eventual outcome is favorable to us. For more information regarding the risks related to our intellectual property, see “Risk Factors—Risks Related to Our Intellectual Property.”

Patent portfolio

As of February 21, 2020, our exclusively owned patent portfolio includes five U.S. issued patents, two pending U.S. provisional patent applications, two pending international (PCT) patent applications, approximately 115 foreign issued patents and approximately 5 pending foreign patent applications. The claims of these owned patents and patent applications are directed toward various aspects of our product candidates and research programs. Specifically, the claims of these patents and patent applications include compositions of matter for product candidates other than APR-246 and a crystal form of APR-246, methods-of-use, drug product formulations, dosing, diagnostics and methods of manufacture.

APR-246 Method of Use Family

As of February 21, 2020, we exclusively own a patent family directed to methods-of-uses of APR-246. This patent family includes one U.S. issued patent and approximately 33 patents granted in Europe (validated in Austria, Belgium, Bulgaria, Switzerland-Lichtenstein, Cyprus, Czech Republic, Germany, Denmark, Estonia, Spain, Finland, France, United Kingdom, Greece, Hungary, Ireland, Iceland, Italy, Lithuania, Luxembourg, Monaco, Netherlands, Poland, Portugal, Romania, Sweden, Slovenia, Slovakia and Turkey), Australia, Canada, India, and Japan. The issued patents in this family are expected to expire in 2025, not giving effect to any potential patent term extensions and patent term adjustments and assuming payment of all appropriate maintenance, renewal, annuity, or other governmental fees.

APR-246 Formulation Family

As of February 21, 2020, we exclusively own a patent family directed to formulations of APR-246. This patent family includes one U.S. issued patent and approximately 42 issued patents in Europe (validated in Austria, Belgium, Switzerland-Lichtenstein, Cyprus, Czech Republic, Germany, Denmark, Estonia, Spain, Finland, France, United Kingdom, Greece, Hungary, Ireland, Italy, Lithuania, Luxembourg, Latvia, Monaco, Malta, Netherlands, Norway, Poland, Portugal, Sweden, Slovakia, San Marino and Turkey), Australia, Brazil, Canada, China, India, Israel, Japan, South Korea, Philippines, Russia, Singapore, and South Africa. This patent family also includes approximately 3 pending patent applications in China, Hong Kong, and Thailand. The granted patents and pending applications, if issued, in this family are expected to expire in 2031, not giving effect to any potential patent term extensions and patent term adjustments and assuming payment of all appropriate maintenance, renewal, annuity, or other governmental fees.

APR-246 Dosing Family

As of February 21, 2020, we exclusively own a pending PCT patent application directed to dosing regimens involving APR-246, which was filed in 2019. This PCT patent application is not eligible to become an issued patent until, among other things, we file a national phase patent application in a PCT contracting state before the expiration of the PCT patent application in that state. If we do not timely file any national phase patent applications, we may lose our priority date with respect to our PCT patent application and any patent protection on the inventions disclosed in our PCT patent application. Any future U.S. patents that may issue from this PCT patent application (assuming the necessary national phase patent applications in U.S. are timely filed and all other applicable requirements are satisfied) are expected to

expire in 2039, not giving effect to any potential patent term extensions and patent term adjustments and assuming payment of all appropriate maintenance, renewal, annuity, or other governmental fees.

APR-246 Process and Solid Form Family

As of February 21, 2020, we exclusively own a pending U.S. provisional patent application directed to improved processes for large scale preparation of APR-246 and to a crystalline solid form comprising APR-246, which was filed in 2019. This provisional patent application is not eligible to become an issued patent until, among other things, we file a non-provisional patent application within 12 months of the filing of our provisional patent application. If we do not timely file any non-provisional patent applications, we may lose our priority date with respect to our provisional patent application and any patent protection on the inventions disclosed in our provisional patent application. Any future U.S. patents that may issue from this provisional patent application (assuming the necessary non-provisional patent applications are timely filed and all other applicable requirements are satisfied) are expected to expire in 2040, not giving effect to any potential patent term extensions and patent term adjustments and assuming payment of all appropriate maintenance, renewal, annuity, or other governmental fees.

Combination Therapy Of APR-246 With A Bcl-2 Inhibitor

As of February 21, 2020, we exclusively own a pending U.S. provisional patent application directed to a method of treatment using a combination therapy of APR-246 with a Bcl-2 inhibitor. This provisional patent application is not eligible to become an issued patent until, among other things, we file a non-provisional patent application within 12 months of the filing of our provisional patent application. If we do not timely file any non-provisional patent applications, we may lose our priority date with respect to our provisional patent application and any patent protection on the inventions disclosed in our provisional patent application. Any future U.S. patents that may issue from this provisional patent application (assuming the necessary non-provisional patent applications are timely filed and all other applicable requirements are satisfied) are expected to expire in 2040, not giving effect to any potential patent term extensions and patent term adjustments and assuming payment of all appropriate maintenance, renewal, annuity, or other governmental fees.

Next-Generation Patent Family/APR-548

As of February 21, 2020, we exclusively own a patent family directed to next-generation p53 reactivators, including APR-548. One pending PCT patent application and one pending national Taiwanese patent application have been filed in 2019 and one European pending patent application has been filed in 2020. In this patent family, the PCT patent application is pending with claims directed to compositions of matter and methods-of-use of APR-548. This PCT patent application is not eligible to become an issued patent until, among other things, we file a national phase patent application in a PCT contracting state before the expiration of the PCT patent application in that state. If we do not timely file any national phase patent applications, we may lose our priority date with respect to our PCT patent application and any patent protection on the inventions disclosed in our PCT patent application. Any future patents that may issue from these patent applications (assuming all applicable requirements are satisfied) are expected to expire in 2039 and 2041, not giving effect to any potential patent term extensions and patent term adjustments and assuming payment of all appropriate maintenance, renewal, annuity, or other governmental fees.

Intellectual property protection

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, the Hatch-Waxman Act permits a patent holder to apply for patent term extension of a patent that covers an FDA-approved drug, which, if granted, can extend the patent term of such patent to compensate for part of the patent term lost during the FDA regulatory review process. This extension can be for up to five years beyond the original expiration date of the patent. The length of the patent term extension is related to the length of time the drug is under regulatory review. Patent term extension cannot extend the remaining term of a patent beyond a total of 14 years from

the date of product approval, only one patent applicable to an approved drug may be extended and only those claims covering the approved drug, a method for using it, or a method for manufacturing it may be extended.

Similar provisions are available in Europe and other non-United States jurisdictions to extend the term of a patent that covers an approved drug. In the future, if and when our product candidates receive FDA approval, we expect to apply for patent term extensions on patents covering those product candidates. While we intend to seek patent term extensions to any of our patents in any jurisdiction where such extensions are available, there is no guarantee that the applicable authorities, including the FDA and the USPTO in the United States, will agree with our assessment of whether such extensions should be granted, and even if granted, the length of such extensions.

In addition to our reliance on patent protection for our inventions, product candidates and research programs, we also rely on trade secrets and confidentiality agreements to protect our technology, know-how and other aspects our business that are not amenable to, or that we do not consider appropriate for, patent protection. Although we take steps to protect our proprietary information and trade secrets, including through contractual means with our employees and consultants, third parties may independently develop substantially equivalent proprietary information and techniques or otherwise gain access to our trade secrets or disclose our technology. Thus, we may not be able to meaningfully protect our trade secrets. It is our policy to require our employees, consultants, outside scientific collaborators, sponsored researchers and other advisors to execute confidentiality agreements upon the commencement of employment or consulting relationships with us. These agreements provide that all confidential information concerning our business or financial affairs developed or made known to the individual or entity during the course of the party's relationship with us is to be kept confidential and not disclosed to third parties except in specific circumstances. In the case of employees, the agreements provide that all inventions conceived by the individual, and which are related to our current or planned business or research and development or made during normal working hours, on our premises or using our equipment or proprietary information, are our exclusive property. However, such confidentiality agreements and invention assignment agreements can be breached and we may not have adequate remedies for any such breach. For more information regarding the risks related to our intellectual property, see "Risk Factors—Risks Related to Our Intellectual Property."

Government Regulation

Government regulation and product approvals

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, post-approval monitoring and reporting, and import and export of drug products. The processes for obtaining marketing 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 in the United States

In the United States, the FDA approves drug products under the Federal Food, Drug, and Cosmetic Act, or FDCA, and implementing regulations. The failure to comply with applicable requirements under the FDCA and other applicable laws at any time during the product development process, approval process or after approval may subject an applicant and/or sponsor to a variety of administrative or judicial sanctions, including refusal by the FDA to approve pending applications, withdrawal of an approval, debarment, imposition of a clinical hold, issuance of warning letters and other types of letters, product recalls, product seizures, total or partial suspension of production or distribution, injunctions, fines, refusals of government contracts, restitution, disgorgement of profits, or civil or criminal investigations and penalties brought by the FDA and the Department of Justice or other governmental entities.

An applicant seeking approval to market and distribute a new drug product in the United States must typically undertake the following:

- completion of preclinical laboratory tests, animal studies and formulation studies in compliance with applicable FDA good laboratory practice, or GLP, regulations;
- submission to the FDA of an IND, which must take effect before human clinical trials begin;
- approval by an independent institutional review board, or IRB, representing each clinical site before each clinical trial may be initiated;
- performance of adequate and well-controlled human clinical trials in accordance with good clinical practices, or GCP, and other applicable regulations to establish the safety and efficacy of the proposed drug product for each proposed indication;
- preparation and submission to the FDA of an NDA requesting marketing for one or more proposed indications;
- review by an FDA advisory committee, where appropriate or if applicable;
- satisfactory completion of one or more FDA inspections of the manufacturing facility or facilities at which the product, or components thereof, are produced to assess compliance with current Good Manufacturing Practices, or cGMP, requirements and to assure that the facilities, methods and controls are adequate to preserve the product's identity, strength, quality and purity;
- satisfactory completion of FDA audits of clinical trial sites to assure compliance with GCPs and the integrity of the clinical data;
- payment of user fees and securing FDA approval of the NDA; 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.

Satisfaction of FDA pre-market approval requirements typically takes many years and the actual time required may vary substantially based upon the type, complexity, and novelty of the product candidate or disease. A clinical hold may occur at any time during the life of an IND and may affect one or more specific trials or all trials conducted under the IND.

Preclinical studies

Before an applicant begins testing a compound with potential therapeutic value in humans, the drug candidate enters the preclinical testing stage. Preclinical studies include laboratory evaluation of product chemistry, toxicity and formulation, as well as *in vitro* and animal studies to assess the potential safety and activity of the drug 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 trials, 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, may continue after the IND is submitted.

The IND and IRB processes

An IND is an exemption from the FDCA that allows an unapproved drug 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 that is not the subject of an approved NDA. In support of a request for an IND, a sponsor must submit, among other things, a protocol for each clinical trial and any subsequent protocol amendments must be submitted to the FDA as part of the IND. The sponsor may be a company seeking to develop the drug or, as in the case of an investigator-initiated trial, the sponsor may be an investigator who is conducting the trial. 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, the FDA may raise concerns or questions about the conduct of the trials as outlined in the IND and impose a clinical hold. In this case, the IND sponsor and the FDA must resolve any outstanding concerns before clinical trials can begin. If the FDA has neither commented on nor questioned the IND within this 30-day period, the clinical trial proposed in the IND may 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. 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 IND requirements must be met unless waived. When the foreign clinical study is not conducted under an IND, the sponsor must ensure that the study complies with certain FDA regulatory requirements in order to use the study as support for an IND or application for marketing approval. Specifically, FDA has promulgated regulations governing the acceptance of foreign clinical trials not conducted under an IND, establishing that such studies will be accepted as support for an IND or application for marketing approval if the study was conducted in accordance with GCP, including review and approval by an independent ethics committee, or IEC, and use of proper procedures for obtaining informed consent from subjects, and the FDA is able to validate the data from the study through an on-site inspection if FDA deems such inspection necessary. The GCP requirements 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 trials, 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. If a marketing application is based solely on foreign clinical data, the FDA requires that the foreign data be applicable to the U.S. population and U.S. medical practice; the studies must have been performed by clinical investigators of recognized competence; and the FDA must be able to validate the data through an on-site inspection or other appropriate means, if the FDA deems such an inspection to be necessary.

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 study at least annually. The IRB must review and approve, among other things, the study protocol and informed consent information to be provided to study 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.

Additionally, some trials are overseen by an independent group of qualified experts organized by the trial sponsor, known as a data safety monitoring board or committee. This group provides authorization for whether or not a trial may move forward at designated check points based on access that only the group maintains to available data from the study. Suspension or termination of development during any phase of clinical trials can occur if it is determined that the

participants or patients are being exposed to an unacceptable health risk. Other reasons for suspension or termination may be made by us based on evolving business objectives and/or competitive climate.

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

Human clinical trials in support of an NDA

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 study protocols detailing, among other things, the inclusion and exclusion criteria, the objectives of the study, the parameters to be used in monitoring safety and the effectiveness criteria to be evaluated.

Human clinical trials are typically conducted in the following sequential phases, which may overlap or be combined:

Phase 1:	The drug is initially introduced into healthy human subjects or, in certain indications such as cancer, patients with the target disease or condition and tested for safety, dosage tolerance, absorption, metabolism, distribution, excretion and, if possible, to gain an early indication of its effectiveness and to determine optimal dosage.
Phase 2:	The drug is administered to a limited patient population to identify possible adverse effects and safety risks, to preliminarily evaluate the efficacy of the product for specific targeted diseases and to determine dosage tolerance and optimal dosage.
Phase 3:	The drug is administered to an expanded patient population, generally at geographically dispersed clinical trial sites, in well-controlled clinical trials to generate enough data to statistically evaluate the efficacy and safety of the product for approval, to establish the overall risk-benefit profile of the product, and to provide adequate information for the labeling of the product.
Phase 4:	Post-approval studies, which are conducted following initial approval, are typically conducted to gain additional experience and data from 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 AEs occur. In addition, IND safety reports must be submitted to the FDA for any of the following: serious and unexpected suspected adverse reactions for which there is evidence to suggest a casual relationship between the drug and the AE; 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 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. Similarly, 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 drug has been associated with unexpected serious harm to patients. 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, and purity 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.

Submission of an NDA to the FDA

Assuming successful completion of required clinical testing and other requirements, the results of the preclinical studies and clinical trials, together with detailed information relating to the product's chemistry, manufacture, controls and proposed labeling, among other things, are submitted to the FDA as part of an NDA requesting approval to market the drug product for one or more indications. Data can come from company-sponsored clinical trials intended to test the safety and effectiveness of a use of a product, or from several alternative sources, including investigator-initiated trials that are not sponsored by company. Under federal law, the submission of NDAs requiring clinical data is additionally subject to an application user fee, which for federal fiscal year 2020 is $2,942,965. The sponsor of an approved NDA is also subject to annual program fees, which for fiscal year 2020 are $325,424 per eligible product.

The FDA conducts a preliminary review of an NDA within 60 days of its receipt and informs the sponsor whether the application is sufficiently complete to permit substantive review. The FDA may request additional information rather than accept an NDA 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. Most such applications are meant to be reviewed within ten months from the filing date, and most applications for "priority review" products are meant to be reviewed within six months of the filing date. 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 NDA, 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 submission, including drug component manufacturing (such as APIs), 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, 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. REMS can include medication guides, physician communication plans for healthcare professionals, and elements to assure safe use, or ETASU. ETASU may include, but are not limited to, special training or certification for prescribing or dispensing, dispensing only under certain circumstances, special monitoring, and the use of patient registries. The FDA may require a REMS before approval or post-approval if it becomes aware of a serious risk associated with use of the product. The requirement for a REMS can materially affect the potential market and profitability of a product.

The FDA is required to refer an application for a novel drug 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.

Fast track, breakthrough therapy and priority review 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 and priority review designation. In May 2014, the FDA published a final Guidance for Industry titled “Expedited Programs for Serious Conditions-Drugs and Biologics,” which provides guidance on the FDA programs that are intended to facilitate and expedite development and review of new product candidates as well as threshold criteria generally applicable to concluding that a product candidate is a candidate for these expedited development and review programs.

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.

Accelerated approval pathway

The FDA may grant accelerated approval to a drug for a serious or life-threatening condition that provides meaningful therapeutic advantage to patients over existing treatments based upon a determination that the drug 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. Drugs 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 drug.

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 drug, 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 drugs 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.

The accelerated approval pathway is contingent on a sponsor's agreement to conduct, in a diligent manner, additional post-approval confirmatory studies to verify and describe the drug's clinical benefit. As a result, a drug 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 withdraw the drug from the market on an expedited basis. All promotional materials for drug candidates approved under accelerated regulations are subject to prior review by the FDA.

The FDA's decision on an NDA

On the basis of the FDA's evaluation of the NDA 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.

Post-approval requirements

Drugs 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, drug manufacturers and other entities involved in the manufacture and distribution of approved drugs 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 NDA holder 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 AEs 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, including total or partial suspension of production, 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. Drugs may be promoted only for the approved indications and in a manner and for uses consistent with the approved labeling. The FDA and other agencies actively enforce the laws and regulations prohibiting the promotion of off-label uses, and a company that is found to have improperly promoted off-label uses may be subject to significant liability.

In addition, the distribution of prescription drug products is subject to the Prescription Drug Marketing Act, or PDMA, which regulates the distribution of drugs and drug samples at the federal level, and sets minimum standards for the registration and regulation of drug distributors by the states. Both the PDMA and state laws limit the distribution of prescription drug product samples and impose requirements to ensure accountability in distribution.

Abbreviated new drug applications for generic drugs

In 1984, with passage of the Hatch-Waxman Amendments to the FDCA, Congress established an abbreviated regulatory scheme allowing 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 API, 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, and the strength of the drug. An applicant may submit an ANDA suitability petition to request the FDA’s prior permission to submit an abbreviated application for a drug that differs from the RLD in route of administration, dosage form, or strength, or for a drug that has one different active ingredient in a fixed-combination drug product (i.e., a drug product with multiple active ingredients). 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 may 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 Amendments, 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, an 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 from the date the NDA is approved, unless the submission is accompanied by a Paragraph IV certification that a listed patent for the RLD is invalid or will not be infringed by the drug that is the subject of the ANDA, 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. 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 only 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; it does, however, block the FDA from approving ANDAs during the period of exclusivity. The FDA typically makes decisions about awards of data exclusivity shortly before a product is approved.

505(b)(2) NDAs

As an alternative path to FDA approval for modifications to formulations or uses of products previously approved by the FDA pursuant to an NDA, an applicant may submit an NDA under Section 505(b)(2) of the FDCA. Section 505(b)(2) was enacted as part of the Hatch-Waxman Amendments and permits the filing of an NDA where at least some of the information required for approval comes from studies not conducted by, or for, the applicant, and for which the applicant has not obtained a right of reference. If the 505(b)(2) applicant can establish that reliance on FDA's previous findings of safety and effectiveness is scientifically and legally appropriate, it may eliminate the need to conduct certain preclinical studies or clinical trials of the new product. The FDA may also require companies to perform additional bridging studies or measurements, including clinical trials, to support the change from the previously approved reference drug. The FDA may then approve the new product candidate for all, or some, of the label indications for which the reference drug has been approved, as well as for any new indication sought by the 505(b)(2) applicant. An RLD's unexpired non-patent exclusivities would also block FDA from accepting or approving 505(b)(2) NDAs in the same way as they apply to ANDAs.

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 or 505(b)(2) 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 or 505(b)(2) application 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 granting final approval of the application 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 applicant. The ANDA or 505(b)(2) application also will not be approved until any applicable non-patent exclusivity listed in the Orange Book for the branded reference drug has expired.

Pediatric studies and exclusivity

Under the Pediatric Research Equity Act of 2003, an NDA or supplement thereto must contain data that are adequate to assess the safety and effectiveness of the drug 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. With enactment of the Food and Drug Administration Safety and Innovation Act of 2012, 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.

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 FDASIA. Unless otherwise required by regulation, the pediatric data requirements do not apply to products with orphan designation.

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 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 may only grant pediatric

exclusivity if existing patent or exclusivity protections for the drug would otherwise expire at least 9 months after the grant of the pediatric exclusivity; FDA has 180 days to make a pediatric exclusivity determination once the NDA sponsor submits study reports required under the written request.

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 product designation before submitting an NDA. If the request is granted, the FDA will disclose the identity of the therapeutic agent and its potential use. Orphan product designation does not convey any advantage in or shorten the duration of the regulatory review and approval process.

If the sponsor of a product with orphan designation receives the first FDA approval for that drug 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 product exclusivity. Orphan product exclusivity means that the FDA may not approve any other applications for the same product for the same indication for seven years, except in certain limited circumstances. If a drug or drug product designated as an orphan product ultimately receives marketing approval for an indication broader than what was designated in its orphan product 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 active ingredient 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. Further, the FDA may approve more than one product for the same orphan indication or disease as long as the products contain different active ingredients. Moreover, competitors may receive approval of different products for the indication for which the orphan product has exclusivity or obtain approval for the same product but for a different indication for which the orphan product has exclusivity.

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 is typically one-half the time between the effective date of an IND and the submission date of an NDA less any time the applicant did not act with due diligence during the period, plus the time between the submission date of an NDA and the ultimate approval date less any time the applicant did not act with due diligence during the period. 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 drug product is eligible for the extension, only those claims covering the approved drug, a method for using it, or a method for manufacturing it may be extended, and the application for the extension must be submitted prior to the expiration of the patent in question. A patent that covers multiple drugs for which approval is sought can only be extended in connection with one of the approvals. The USPTO reviews and approves the application for any patent term extension or restoration in consultation with the FDA. Similar provisions are available in Europe and other foreign jurisdictions to extend the term of a patent that covers an approved drug. In the future, if and when our products receive FDA approval, we expect to apply for patent term extensions on patents covering those products. We plan to seek patent term extensions to any of our issued patents in any jurisdiction where these are available, however there is no guarantee that the applicable authorities, including the FDA in the United States, will agree with our assessment of whether such extensions should be granted, and if granted, the length of such extensions. For more information regarding the risks related to our intellectual property, see "Risk Factors—Risks Related to Our Intellectual Property."

FDA approval and regulation of companion diagnostics

A therapeutic product may rely upon an *in vitro* companion diagnostic for use in selecting the patients that will be more likely to respond to that therapy. 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, for novel drugs, a companion diagnostic device and its corresponding therapeutic should be approved or cleared contemporaneously by the FDA for the use indicated in the therapeutic product's labeling. In July 2016, the FDA issued a draft guidance intended to assist sponsors of the drug therapeutic and *in vitro* companion diagnostic device on issues related to co-development of the products.

If FDA determines that a companion diagnostic device is essential to the safe and effective use of a novel therapeutic product or indication, FDA generally will not approve the therapeutic product or new therapeutic product indication if the companion diagnostic device is not approved or cleared for that indication. Approval or clearance of the companion diagnostic device will ensure that the device has been adequately evaluated and has adequate performance characteristics in the intended population. The review of *in vitro* companion diagnostics in conjunction with the review of our therapeutic treatments for cancer will, therefore, likely involve coordination of review by the FDA's Center for Drug Evaluation and Research and the FDA's Center for Devices and Radiological Health Office of In Vitro Diagnostics Device Evaluation and Safety.

Under the FDCA, *in vitro* diagnostics, including companion diagnostics, are regulated as medical devices. In the United States, the FDCA and its implementing regulations, and other federal and state statutes and regulations govern, among other things, medical device design and development, preclinical and clinical testing, premarket clearance or approval, registration and listing, manufacturing, labeling, storage, advertising and promotion, sales and distribution, export and import, and post-market surveillance. Unless an exemption applies, diagnostic tests require marketing clearance or approval from the FDA prior to commercial distribution. The two primary types of FDA marketing authorization applicable to a medical device are premarket notification, also called 510(k) clearance, and premarket approval, or PMA. The FDA has generally required *in vitro* companion diagnostics intended to select the patients who will respond to cancer treatment to obtain a PMA for that diagnostic simultaneously with approval of the drug. We expect that any companion diagnostic developed for use with APR-246 will utilize the PMA pathway.

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 of $340,995 for most PMAs for FY 2020. In addition, PMAs for certain devices must generally include the results from extensive preclinical and adequate and well-controlled clinical trials to establish the safety and effectiveness of the device for each indication for which FDA approval is sought. In particular, for a diagnostic, a PMA application typically requires data regarding analytical and clinical validation studies. As part of the PMA review, the FDA will typically inspect the manufacturer's facilities for compliance with the Quality System Regulation, or QSR, which imposes elaborate testing, control, documentation and other quality assurance requirements.

PMA approval is not guaranteed, and the FDA may ultimately respond to a PMA submission with a not approvable determination based on deficiencies in the application and require additional clinical trial or other data that may be expensive and time-consuming to generate and that can substantially delay approval. If the FDA's evaluation of the PMA application is favorable, the FDA typically issues an approvable letter requiring the applicant's agreement to specific conditions, such as changes in labeling, or specific additional information, such as submission of final labeling, in order to secure final approval of the PMA. If the FDA's evaluation of the PMA or manufacturing facilities is not favorable, the FDA will deny approval of the PMA or issue a not approvable letter. A not approvable letter will outline the deficiencies in the application and, where practical, will identify what is necessary to make the PMA approvable. The FDA may also determine that additional clinical trials are necessary, in which case the PMA approval may be delayed for several months or years while the trials are conducted and then the data submitted in an amendment to the PMA. If the FDA concludes that the applicable criteria have been met, the FDA will issue a PMA for the approved indications, which can be more limited than those originally sought by the applicant. The PMA can include post-approval conditions that the FDA believes necessary to ensure the safety and effectiveness of the device, including, among other things, restrictions on labeling, promotion, sale and distribution. Once granted, PMA approval may be withdrawn by the FDA if compliance with post approval requirements, conditions of approval or other regulatory standards are not maintained or problems are identified following initial marketing.

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 U.S.

The 21st Century Cures Act

On December 13, 2016, the 21st Century Cures Act, or the Cures Act, became law. The Cures Act is designed to modernize and personalize healthcare, spur innovation and research, and streamline the discovery and development of new therapies through increased federal funding of particular programs. It authorizes increased funding for the FDA to spend on innovation projects. The new law also amends the PHSA to reauthorize and expand funding for the NIH. The Cures Act establishes the NIH Innovation Fund to pay for the cost of development and implementation of a strategic plan, early stage investigators and research. It also charges NIH with leading and coordinating expanded pediatric research. Further, the Cures Act directs the Centers for Disease Control and Prevention to expand surveillance of neurological diseases.

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

Regulations outside the United States

Regulations and procedures governing approval of drug products in the EU

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 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. Specifically, the process governing approval of drug products in the EU generally follows the same lines as in the United States and involves satisfactorily completing preclinical studies and adequate and well-controlled clinical trials to establish the safety and efficacy of the product for each proposed indication, as well as the submission to the relevant competent authorities of a marketing authorisation application, or MAA, and actual granting of a marketing authorization by these authorities before the product can be marketed and sold in the EU.

Clinical Trial Approval. Pursuant to the currently applicable Clinical Trials Directive 2001/20/EC and the Directive 2005/28/EC on Good Clinical Practice, 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 a 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 must be accompanied by an investigational drug 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 will replace the current Clinical Trials Directive 2001/20/EC. To ensure that the rules for clinical trials are identical throughout the EU, the new EU clinical trials legislation was passed as a regulation that is directly applicable in all EU member states without the need for implementation into the member states' national laws. All clinical trials performed in the EU are required to be conducted in accordance with the Clinical Trials Directive 2001/20/EC until the new Clinical Trials Regulation (EU) No 536/2014 becomes applicable. According to the European Commission, the new Clinical Trials Regulation is currently expected to become applicable in late2021 or 2022. The Clinical Trials Directive 2001/20/EC will, however, still apply three years from the date of entry into application of the Clinical Trials Regulation to (i) clinical trials applications submitted before the entry into application and (ii) clinical trials applications submitted within one year after the entry into application if the sponsor opts for old system.

The new Clinical Trials Regulation aims to simplify and streamline the approval of clinical trial in the EU. The main characteristics of the regulation include: a streamlined application procedure via a single entry point, the EU portal; a single set of documents to be prepared and submitted for the application as well as simplified reporting procedures that will spare sponsors from submitting broadly identical information separately to various bodies and different member states; a harmonized procedure for the assessment of applications for clinical trials, which is divided in two parts. Part I is assessed jointly by all member states concerned. Part II is assessed separately by each member state concerned; strictly defined deadlines for the assessment of clinical trial applications; and the involvement of the ethics committees in the assessment procedure in accordance with the national law of the member state concerned but within the overall timelines defined by the Clinical Trials Regulation.

Marketing Authorization. To obtain a marketing authorization for a product under EU regulatory systems, an applicant must submit an MAA either under a centralized procedure administered by the EMA or one of the procedures administered by competent authorities in EU member states (decentralized procedure, national procedure or mutual recognition procedure). A marketing authorization may be granted only to an applicant established in the EU. In the case of pediatric patients, Regulation (EC) No 1901/2006 provides that prior to obtaining a marketing authorization in the EU, applicants have to demonstrate compliance with all measures included in an EMA-approved Pediatric Investigation Plan, or PIP, covering all subsets of the pediatric population, unless the EMA has granted (1) a product-specific waiver, (2) a class waiver or (3) a deferral for one or more of the measures included in the PIP.

The centralized procedure provides for the grant of a single marketing authorization by the European Commission that is valid for all EU member states. Pursuant to Regulation (EC) No 726/2004, the centralized procedure is compulsory for specific products, including for medicines produced by certain biotechnological processes, products designated as orphan drug products, advanced therapy products and products with a new active substance indicated for the treatment of certain diseases, including products for the treatment of cancer. For products with a new active substance indicated for the treatment of other diseases and products that are highly innovative or for which a centralized process is in the interest of patients, the centralized procedure may be optional.

Under the centralized procedure, the Committee for Medicinal Products for Human Use, or the CHMP, established at the EMA is responsible for conducting the initial assessment of a product. The CHMP is also responsible for several post-authorization and maintenance activities, such as the assessment of modifications or extensions to an existing marketing authorization. Under the centralized procedure in the EU, the maximum timeframe for the evaluation of an MAA is 210 days, excluding clock stops, when additional information or written or oral explanation is to be provided by the applicant in response to questions of the CHMP. Accelerated evaluation might be granted by the CHMP in exceptional cases, when a drug product is of major interest from the point of view of public health and in particular from the viewpoint of therapeutic innovation. If the CHMP accepts such request, the time limit of 210 days will be reduced to 150 days but it is possible that the CHMP can revert to the standard time limit for the centralized procedure if it considers that it is no longer appropriate to conduct an accelerated assessment.

Regulatory data protection in the EU. 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 an 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 drug product can be marketed until the expiration of the market exclusivity. The overall ten-year period will be extended to a maximum of 11 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 their authorization, are 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 nevertheless could also 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.

Periods of authorization and renewals. A marketing authorization shall be valid for five years in principle and the marketing authorization may be renewed after five years on the basis of a re-evaluation of the risk-benefit balance by the EMA or by the competent authority of the authorizing member state. To this end, the marketing authorization holder must provide the EMA or the competent authority with a consolidated version of the file in respect of quality, safety and efficacy, including all variations introduced since the marketing authorization was granted, at least six months before the marketing authorization ceases to be valid. Once renewed, the marketing authorization shall be valid for an unlimited period, unless the European Commission or the competent authority decides, on justified grounds relating to pharmacovigilance, to proceed with one additional five-year renewal. Any authorization which is not followed by the actual placing of the drug on the EU market (in case of centralized procedure) or on the market of the authorizing member state within three years after authorization ceases to be valid (the so-called sunset clause).

Orphan drug designation and exclusivity. Regulation (EC) No 141/2000 on orphan drug products provides that a drug shall be designated as an orphan drug if its sponsor can establish that the product is intended for the diagnosis, prevention or treatment of 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 that the product is intended for the diagnosis, prevention or treatment of a life-threatening, seriously debilitating or serious and chronic condition in the EU and that without incentives it is unlikely that the marketing of the drug in the EU would generate sufficient return to justify the necessary investment. 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 drug will be of significant benefit to those affected by that condition.

Regulation (EC) No 847/2000 sets out criteria and procedures governing designation of orphan drugs in the EU. Specifically, an application for designation as an orphan product can be made any time prior to the filing of an application for approval to market the product. Marketing authorization for an orphan drug leads to a ten-year period of market exclusivity. During this market exclusivity period, the EMA or the member state competent authorities, cannot accept another application for a marketing authorization, or grant a marketing authorization, for a similar drug product for the same indication. The period of market exclusivity is extended by two years for medicines that have also complied with an agreed PIP.

This period may, however, be reduced to six years if, at the end of the fifth year, it is established that the product no longer meets the criteria for orphan drug designation, for example because the product is sufficiently profitable not to justify market exclusivity. Market exclusivity can be revoked only in very selected cases, such as consent from the marketing authorization holder, inability to supply sufficient quantities of the product, demonstration of "clinical superiority" by a similar drug product, or, after a review by the Committee for Orphan Medicinal Products, requested by a member state in the fifth year of the marketing exclusivity period (if the designation criteria are believed to no longer apply).

Regulatory requirements after a marketing authorization has been obtained. In case an authorization for a drug in the EU is obtained, the holder of the marketing authorization is required to comply with a range of requirements applicable to the manufacturing, marketing, promotion and sale of drug products. These include:

- Compliance with the EU's stringent pharmacovigilance or safety reporting rules, pursuant to which post-authorization studies and additional monitoring obligations can be imposed, has to be ensured.

- The manufacturing of authorized drugs, for which a separate manufacturer's license is mandatory, must also be conducted in strict compliance with the EMA's GMP requirements and comparable requirements of other regulatory bodies in the EU, which mandate the methods, facilities and controls used in manufacturing, processing and packing of drugs to assure their safety and identity.

- 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.

Authorization to market companion diagnostics in the EU.

In the European Economic Area, or EEA, *in vitro* medical devices are currently required to conform with the essential requirements of the European Union Directive on *in vitro* diagnostic medical devices (Directive No 98/79/EC, as amended). To demonstrate compliance with the essential requirements, the manufacturer must undergo a conformity assessment procedure. The conformity assessment varies according to the type of medical device and its classification. The conformity assessment of *in vitro* diagnostic medical devices can require the intervention of an accredited EEA Notified Body. If successful, the conformity assessment concludes with the drawing up by the manufacturer of an EC Declaration of Conformity entitling the manufacturer to affix the CE mark to its products and to sell them throughout the EEA. On April 5, 2017, the EU adopted the new In Vitro Device Regulation (EU) 2017/746, or IVDR, which repeals and replaces Directive No 98/79/EC. Unlike directives, which must be implemented into the national laws of the EU member states, a regulation is directly applicable, i.e., without the need for adoption of EU member state laws implementing them, in all EEA member states. The IVDR, among other things, is intended to establish a uniform, transparent, predictable and sustainable regulatory framework across the EU for *in vitro* diagnostic medical devices and ensure a high level of safety and health while supporting innovation. The IVDR will not become fully applicable until five years following its entry into force. Once applicable, the IVDR will among other things:

- strengthen the rules on placing devices on the market and reinforce surveillance once they are available;

- establish explicit provisions on manufacturers' responsibilities for the follow-up of the quality, performance and safety of devices placed on the market;

- improve the traceability of medical devices throughout the supply chain to the end-user or patient through a unique identification number; and

- set up a central database to provide patients, healthcare professionals and the public with comprehensive information on products available in the EU.

Brexit and the regulatory framework in the United Kingdom

On June 23, 2016, the electorate in the U.K., voted in favor of leaving the EU, commonly referred to as Brexit. The U.K. government communicated the notice of withdrawal to the EU on March 29, 2017. A withdrawal agreement and a political declaration were agreed at the European Council on October 17, 2019, on the terms of which the U.K. left the EU on January 31, 2020. A transition period is currently running, during which the U.K. is, with some exceptions, treated as a member of the EU. It is unclear exactly how the United Kingdom's exit of the European Union may affect the recognition of European-wide marketing authorizations by the United Kingdom, as this will be dependent on the outcome of ongoing negotiations between the European Union and the United Kingdom during the transition period which is expected to terminate on December 31, 2020. Since the regulatory framework for drug products in the U.K. covering quality, safety and efficacy of drug products, clinical trials, marketing authorization, commercial sales and distribution of drug 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 U.K.

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. Patients and healthcare providers are unlikely to use our products unless third-party payor coverage is provided and reimbursement by such payor is adequate to cover a significant portion of the cost of our products. Significant uncertainty exists as to the coverage and reimbursement status of products approved by the FDA and other comparable government authorities. Even if our product candidates are approved, sales of our products will depend, in part, on the extent to which third-party payors, including federal health care programs in the United States, such as Medicare and Medicaid, and commercial health insurers and managed care organizations, provide coverage and establish adequate reimbursement levels for such products. 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 a payor will pay for the product once coverage is approved. Third-party payors are increasingly challenging the prices charged for, examining the medical necessity of, 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. Coverage and reimbursement by a third-party payor may depend upon a number of factors, including, without limitation, the third-party payor's determination that use of a therapeutic product is:

- a covered benefit under its health plan;
- safe, effective and medically necessary;
- appropriate for the specific patient;
- cost-effective; and
- neither experimental nor investigational.

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. Obtaining coverage and reimbursement approval of a product from a government or other third-party payor is a time-consuming and costly process that could require us to provide to each payor supporting scientific, clinical and cost-effectiveness data for the use of our products on a payor-by-payor basis, with no assurance that coverage and adequate reimbursement will be obtained. Nonetheless, product candidates may not be considered medically necessary or cost effective. A decision by a third-party payor not to cover our product candidates could reduce health care provider prescribing and/or patient utilization of our products once approved and have a material adverse effect on our 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 established. 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. Third-party coverage and reimbursement may not be available to enable us to maintain price levels sufficient to realize an appropriate return on our investment in product development.

In addition, prices for drugs may be reduced by mandatory discounts or rebates required by federal health care programs (such as the Medicaid Drug Rebate Program and the 340B Drug Pricing Program) or discounts and rebates requested by private payors. In addition, any future relaxation of laws that presently restrict imports of drugs from countries where they may be sold at lower prices than in the United States may also impact the pricing of drugs. It is difficult to predict how Medicare coverage and reimbursement policies will be applied to products for which the company receives marketing approval in the future and coverage and reimbursement under different federal health care programs is not always consistent. Further, private payors often follow the coverage and reimbursement policies established under Medicare. If reimbursement is not available or is available only at limited levels, we may not be able to successfully commercialize our products for which we receive marketing approval.

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 our product candidates will face 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 marketing approval for a product and may require us to conduct a clinical trial that compares the cost effectiveness of our product candidates or products to other available therapies. The conduct of such a clinical trial could be expensive and result in delays in our commercialization efforts.

In the EU, pricing and reimbursement schemes vary widely from member state to member state. 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 (so called health technology assessment, or HTA) in order to obtain reimbursement or pricing approval. 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 healthcare 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 (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 drug products will allow favorable reimbursement and pricing arrangements for any of our products, if approved in those countries.

Healthcare law and regulation

In the United States, our activities are potentially subject to regulation by various federal, state and local authorities in addition to the FDA, including but not limited to, the Centers for Medicare and Medicaid Services, or CMS, other divisions of the U.S. Department of Health and Human Services (such as the Office of Inspector General and the Health Resources and Service Administration), the U.S. Department of Justice, and individual U.S. Attorney offices, and state and local governments. For example, sales, marketing and scientific/educational grant programs are subject to the anti-fraud and abuse provisions of the Social Security Act and the false claims laws, and may have to comply with the privacy and security provisions of the HIPAA (defined below), and similar state laws, each as amended, as applicable. 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 these broadly applicable healthcare laws and regulations that may constrain our business and/or financial arrangements.

The applicable federal and state healthcare laws and regulations, include, without limitation, the following:

- *The Federal Anti-Kickback Statute*—An intent-based federal criminal statute that prohibits, among other things, any person from knowingly and willfully soliciting, offering, receiving or paying 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, in whole or in part, by a federal health care program, such as Medicare and Medicaid. The term "remuneration" has been broadly interpreted to include anything of value. The

PPACA, among other things, amended the intent requirement of the federal Anti-Kickback Statute, to clarify that a person or entity need not have actual knowledge of this statute or specific intent to violate it. The Anti-Kickback Statute applies to arrangements between pharmaceutical manufacturers on the one hand and individuals, such as prescribers, patients, purchasers, and formulary managers on the other hand, including, for example, consulting/speaking arrangements, discount and rebate offers, grants, charitable contributions, and patient support offerings, among others. A conviction for violation of the Anti-Kickback Statute can result in criminal fines and/or imprisonment and requires mandatory exclusion from participation in federal health care programs. Exclusion may also be imposed if the government determines that an entity has committed acts that are prohibited by the Anti-Kickback Statute. Although there are a number of statutory exceptions and regulatory safe harbors to the federal Anti-Kickback Statute that protect certain common industry practices from prosecution, the exceptions and safe harbors are narrowly drawn, and arrangements may be subject to scrutiny or penalty if they do not fully satisfy all elements of an available exception or safe harbor. The Anti-Kickback Statute safe harbors are the subject of possible regulatory reforms. Any changes to the safe harbors may impact our future contractual and other arrangements with pharmacy benefit managers, group purchasing managers, third-party payors, wholesalers and distributors, healthcare providers and prescribers, and other entities, as well as our future pricing strategies.

- *The Federal Civil False Claims Act*—Imposes 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 to a federal healthcare program or knowingly making using or causing to be made or used 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 $11,181 to $22,363 per false claim or statement for penalties assessed after January 29, 2018, with respect to violations occurring after November 2, 2015. Pharmaceutical companies have been investigated and/or subject to government enforcement actions asserting liability under the federal civil False Claims Act in connection with their alleged off-label promotion of drugs, purportedly concealing price concessions in the pricing information submitted to the government for government price reporting purposes (e.g., under the Medicaid Drug Rebate Program), and allegedly providing free product to customers with the expectation that the customers would bill federal health care programs for the product. In addition, the government may assert that a claim including items or services resulting from a violation of the federal Anti-Kickback Statute constitutes a false or fraudulent claim for purposes of the federal False Claims Act. As a result of a modification made by the Fraud Enforcement and Recovery Act of 2009, a claim includes “any request or demand” for money or property presented to the U.S. government. In addition, manufacturers can be held liable under the federal False Claims Act even when they do not submit claims directly to government payors if they are deemed to “cause” the submission of false or fraudulent claims. There is also the Federal Criminal False Claims Act, which is similar to the Federal Civil False Claims Act and imposes criminal liability on those that make or present a false, fictitious or fraudulent claim to the federal government.

- *The Federal Criminal Statute on False Statements Relating to Health Care Matters*—Makes it a crime to knowingly and willfully falsify, conceal, or cover up a material fact, make any materially false, fictitious, or fraudulent statements or representations, or make or use any materially false writing or document knowing the same to contain any materially false, fictitious, or fraudulent statement or entry in connection with the delivery of or payment for healthcare benefits, items, or services.

- *HIPAA Criminal Federal Health Care Fraud Statute*—Enacted as part of the Health Insurance Portability and Accountability Act of 1996 (“HIPPA”), makes it a crime to knowingly and willfully execute, or attempt to execute, a scheme or artifice to defraud any health care benefit program or to obtain, by means of false or fraudulent pretenses, representations, or promises, any of the money or property owned by, or under the custody or control of any health care benefit program in connection with the delivery of or payment for healthcare benefits, items, or services.

- *The Federal Civil Monetary Penalties Law*—Authorizes the imposition of substantial civil monetary penalties against an entity, such as a pharmaceutical manufacturer, that engages in activities including, among others (1) knowingly presenting, or causing to be presented, a claim for services not provided as claimed or that is otherwise false or fraudulent in any way; (2) arranging for or contracting with an individual or entity that is excluded from participation in federal healthcare programs to provide items or services reimbursable by a federal healthcare program; (3) violations of the federal Anti-Kickback Statute; or (4) failing to report and return a known overpayment.

- *HIPAA Health Information Privacy and Security*—HIPAA, as amended by the federal Health Information Technology for Economic and Clinical Health Act ("HITECH") imposes privacy, security, and breach reporting obligations on certain covered entity healthcare providers, health plans, and healthcare clearinghouse as well as their business associates that perform certain services involving the use or disclosure of individually identifiable protected health information, including, among other requirements, to implement certain policies and procedures, to support certain substantive rights of patients, mandatory contractual terms and technical safeguards to protect the privacy, security and transmission of individually identifiable health information, and require notification to affected individuals and regulatory authorities of certain breaches of security of individually identifiable health information. HITECH also created tiers of civil monetary penalties, amended HIPAA to make civil and criminal penalties directly applicable to business associates, and gave state attorneys general new authority to file civil actions for damages or injunctions in U.S. federal courts to enforce the federal HIPAA laws and seek attorneys' fees and costs associated with pursuing federal civil actions.

- *The Federal Physician Payments Sunshine Act*—Requires "applicable manufacturers" of drugs, devices, biologics, and medical supplies for which payment is available under Medicare, Medicaid or the State Children's Health Insurance Program, among others, to track and report annually to the federal government (for disclosure to the public) certain payments and other transfers of value they make to "covered recipients." The term covered recipients includes physicians, teaching hospitals, and, for reports submitted on or after January 1, 2022, physician assistants, nurse practitioners, clinical nurse specialists, certified nurse anesthetists, and certified nurse midwives. Failure to submit required information may result in civil monetary penalties.

- *The Federal Food, Drug and Cosmetic Act*—A set of laws, which prohibits, among other things, the adulteration or misbranding of drugs, biologics and medical devices.

- *Analogous State and Foreign Laws*—There are state and foreign law equivalents of the above federal laws, such as the Anti-Kickback Statute and the False Claims Act, which may apply to items or services reimbursed by any third-party payor, including commercial insurers (i.e., so-called "all-payor anti-kickback laws"), as well as state and foreign laws that govern the privacy and security of health information or personally identifiable information in certain circumstances, including state health information privacy and data breach notification laws which govern the collection, use, disclosure, and protection of health-related and other personal information, many of which differ from each other in significant ways and, with respect to state laws, are often not pre-empted by HIPAA, thus requiring additional compliance efforts.

- *State and Foreign Laws Regulating Pharmaceutical Manufacturer Compliance Programs, Drug Price Transparency, and Other Practices*—Some state and foreign laws require pharmaceutical companies to implement compliance programs, comply with the pharmaceutical industry's voluntary compliance guidelines and the relevant compliance guidance promulgated by the federal government, or to track and report gifts, compensation, or other remuneration to physicians and other healthcare providers. Several U.S. states and localities have enacted legislation requiring pharmaceutical companies to establish marketing compliance programs, file periodic reports, and/or make periodic public disclosures on sales, marketing, pricing, clinical trials, and other activities. Other state laws prohibit certain marketing-related activities including the provision of gifts, meals or other items to certain healthcare providers, and restrict the ability of manufacturers to offer co-pay support to patients for certain prescription drugs. In addition, several recently passed state laws require disclosures related to state agencies and/or commercial purchasers with

respect to certain price increases that exceed a certain level as identified in the relevant statutes. Some of these laws and regulations contain ambiguous requirements that government officials have not yet clarified. Given the lack of clarity in the laws and their implementation, our reporting actions could be subject to the penalty provisions of the pertinent federal and state laws and regulations.

We expect that one or more of our products, if approved, may be eligible for coverage under Medicare, the federal health care program that provides health care benefits to the aged and disabled, including coverage for outpatient services and supplies, such as certain drug products, that are medically necessary to treat a beneficiary's health condition. In addition, one or more of our products, if approved, may be covered and reimbursed under other federal health care programs, such as Medicaid and the 340B Drug Pricing Program. The Medicaid Drug Rebate Program requires pharmaceutical manufacturers to enter into and have in effect a national rebate agreement with the Secretary of the Department of Health and Human Services and pay quarterly rebates based on utilization of the manufacturer's drugs under the program as a condition for states to receive federal matching funds for the manufacturer's outpatient drugs furnished to Medicaid patients. Under the 340B Drug Pricing Program, the manufacturer must extend discounts to entities that participate in the program. As part of the requirements to participate in these government programs, many pharmaceutical manufacturers must calculate and report certain price reporting metrics to the government, such as average manufacturer price and best price.

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, guidance, case law or other applicable law. 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, exclusion from participation in federal health care programs, such as Medicare and Medicaid, disgorgement, reputational harm, additional oversight and reporting obligations pursuant to a corporate integrity agreement or similar agreement to resolve allegations of non-compliance with applicable laws and regulations, and the curtailment or restructuring of our operations, any of which could adversely affect our ability to market our products, if approved, and adversely impact our financial results. Although effective compliance programs can mitigate the risk of investigation and prosecution for violations of these laws and regulations, these risks cannot be eliminated entirely. Any action against us for an alleged or suspected violation could cause us to incur significant legal expenses and could divert our management's attention from the operation of our business, even if our defense is successful. If any of the physicians or other healthcare providers or entities with whom we expect to do business is found not to be in compliance with applicable laws, it may be costly to us in terms of money, time and resources, and they may be subject to criminal, civil or administrative sanctions, including exclusions from government-funded healthcare programs.

U.S. healthcare reform

In the United States and some foreign jurisdictions, there have been and continue to be 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, or the ability of our future collaborators, to effectively sell any drugs for which we, or they, 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 additional downward pressure on the price that we, or our future collaborators, may receive for any approved drugs. For example, the Patient Protection and Affordable Care Act, as emended by the Health Care and Education Reconciliation Act (collectively, "PPACA") has substantially changed and continues to impact healthcare financing and delivery by both government payors and private insurers. Among the PPACA provisions of importance to the pharmaceutical industry, in addition to those otherwise described above, are the following:

- 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 federal programs identified in the PPACA;

- expansion of beneficiary eligibility criteria for Medicaid programs by, among other things, allowing states to offer Medicaid coverage to certain individuals with income at or below 138% of the federal poverty level, thereby potentially increasing manufacturers' Medicaid rebate liability;

- expansion of 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" for calculating and reporting Medicaid drug rebates on outpatient prescription drug prices;

- extension of manufacturers' Medicaid rebate liability to covered drugs dispensed to individuals who are enrolled in Medicaid managed care organizations;

- a new methodology by which rebates owed by manufacturers under the Medicaid Drug Rebate Program are calculated for drugs that are inhaled, infused, instilled, implanted or injected;

- expansion of the types of entities eligible for the 340B drug discount program;

- establishment of the Medicare Part D coverage gap discount program that, as a condition for the manufacturers outpatient drugs to be covered under Medicare Part D, requires manufacturers to provide a now 70% point-of-sale-discount off the negotiated price of applicable brand drugs to eligible beneficiaries during their coverage gap period;

- establishment of the Center for Medicare and Medicaid Innovation within the Centers for Medicare and Medicaid Services to test innovative payment and service delivery models to lower Medicare and Medicaid spending, potentially including prescription drug spending;

- creation of the Patient-Centered Outcomes Research Institute to oversee, identify priorities in, and conduct comparative clinical effectiveness research, along with funding for such research;

- reporting of certain financial arrangements between manufacturers of drugs, biologics, devices, and medical supplies and physicians and teaching hospitals under the Physician Payments Sunshine Act; and

- annual reporting of certain information regarding drug samples that manufacturers and distributors provide to licensed practitioners.

There have been judicial and Congressional challenges to certain aspects of the PPACA, as well as efforts by the Trump Administration to repeal or replace certain aspects of the PPACA that contribute to regulatory uncertainty that could affect the profitability of our products. While Congress has not enacted legislation to comprehensively repeal the PPACA, at least two bills affecting the PPACA have been signed into law, including the repeal, effective January 1, 2019, of the tax-based shared responsibility payment imposed by the PPACA on certain individuals who fail to maintain qualifying health coverage for all or part of a year, which is commonly referred to as the "individual mandate." In December 2018, a federal district court in Texas ruled that the PPACA's individual mandate, without the penalty that was repealed effective January 1, 2019, was unconstitutional and could not be severed from the PPACA. As a result, the court ruled the remaining provisions of the PPACA were also invalid. The Fifth Circuit Court of Appeals affirmed the district court's ruling that the individual mandate was unconstitutional, but it remanded the case back to the district court for further analysis of whether the mandate could be severed from the PPACA (i.e., whether the entire PPACA was therefore also unconstitutional). The Supreme Court of the United States granted certiorari on March 2, 2020, and the case is expected to be decided in 2021.

Since January 2017, President Trump has also signed several Executive Orders and other directives designed to delay the implementation of certain provisions of the PPACA or otherwise circumvent some of the requirements mandated by the PPACA. For example, on January 22, 2018, President Trump signed a continuing resolution on appropriations for fiscal year 2018 that delayed the implementation of certain fees mandated by the PPACA, including the so-called "Cadillac"

tax on certain high-cost employer-sponsored health insurance plans, the annual fee imposed on certain health insurance providers, and the medical device excise tax on non-exempt medical devices.

Effective January 1, 2019, the Bipartisan Budget Act of 2018, among other things, further amended portions of the Social Security Act implemented as part of the PPACA to increase from 50% to 70% the point-of-sale discount that pharmaceutical manufacturers participating in the Coverage Gap Discount Program must provide to eligible Medicare Part D beneficiaries during the coverage gap phase of the Part D benefit, commonly referred to as the “donut hole,” and to reduce standard beneficiary cost sharing in the coverage gap from 30% to 25% in most Medicare Part D plans. In the future, there may be additional challenges and/or amendments to the PPACA. It remains to be seen precisely what any new legislation will provide, when or if it will be enacted, and what impact it will have on the availability and cost of healthcare items and services, including drug products.

More recently, the cost of prescription pharmaceuticals has been the subject of considerable discussion in the United States. Congress has begun developing legislation and the Trump Administration has proposed and begun implementing regulatory reforms to further increase transparency around prices and price increases, lower out-of-pocket costs for consumers, and decrease spending on prescription drugs by government programs. Congress has conducted or is in the process of conducting inquiries into the prescription drug industry’s pricing practices. While several proposed reform measures will require Congress to pass legislation to become effective, Congress and the Trump Administration have each indicated that it will continue to seek new legislative and/or regulatory measures to address prescription drug costs. At the state level, legislatures are increasingly passing legislation and states are implementing regulations designed to control spending on and patient out-of-pocket costs for drug products. Implementation of cost containment measures or other healthcare reforms that affect the pricing and/or availability of drug products may impact our ability to generate revenue, attain or maintain profitability, or commercialize products for which we may receive regulatory approval in the future.

We expect that these and other healthcare reform measures that may be adopted in the future may result in more rigorous coverage criteria and/or new payment methodologies, and place additional downward pressure on the price that we receive for any approved product and/or the level of reimbursement physicians and other healthcare providers receive for administering any approved product we might bring to market. Reductions in reimbursement levels and imposition of more rigorous coverage criteria or new payment methodologies may negatively impact the prices we receive or the frequency with which our products are prescribed or administered. Any coverage or reimbursement policies instituted by Medicare or other federal health care programs may result in a similar policies from private payors. The implementation of cost containment measures or other healthcare reforms may affect our ability to generate revenue, attain or maintain profitability, or commercialize our drug candidates. 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 drug candidates or additional pricing pressures.

Employees

As of December 31, 2019, we had 13 full-time employees. Of the workforce, 8 employees are directly engaged in research and development with the rest providing administrative, business and operations support. We are not bound by any collective bargaining agreements. We consider the relationship with our employees to be good. We also use outside consultants and contractors with unique expertise and skills for limited engagements. As of December 31, 2019, we utilized multiple outside consultants or contractors that represented approximately 4 full-time equivalents to supplement our full-time workforce.

Corporate Information

We were incorporated in Delaware in May 2019. Aprea Therapeutics AB was originally incorporated in 2002 and commenced principal operations in 2006. On September 20, 2019, we consummated a reorganization, pursuant to which all of the issued and outstanding stock and options of Aprea Therapeutics AB were exchanged for common stock, preferred stock or options, as applicable, of Aprea Therapeutics, Inc. As a result, Aprea Therapeutics AB became a wholly-owned subsidiary of Aprea Therapeutics, Inc. Our corporate headquarters are located at 535 Boylston Street,

Boston Massachusetts 02116, and our telephone number is (617) 463-9385. In addition, we have research facilities in Stockholm, Sweden.

Available Information

Our corporate website address is www.aprea.com. Information contained on or accessible through our website are not part of this Annual Report on Form 10-K, and inclusion of our website address in this annual report is an inactive textual reference only. We make our Annual Report on Form 10-K, quarterly reports on Form 10-Q, current reports on Form 8-K and all amendments to those reports available free of charge on our website as soon as reasonably practicable after we file such reports with, or furnish such reports to, the Securities and Exchange Commission, or SEC.

We are an "emerging growth company," as defined in the Jumpstart Our Business Startups Act of 2012 ("JOBS Act"). We will remain an emerging growth company until the earlier of (1) the last day of the fiscal year (a) following the fifth anniversary of the completion of our initial public offering, (b) in which we have total annual gross revenue of at least $1.07 billion, or (c) in which we are deemed to be a large accelerated filer, which means the market value of our common stock that is held by non-affiliates exceeded $700 million as of the prior March 31st, and (2) the date on which we have issued more than $1.0 billion in non-convertible debt during the prior three-year period.

We are also a "smaller reporting company," as such term is defined in Rule 12b-2 of the Exchange Act, meaning that the market value of our common stock held by non-affiliates is less than $700 million and our annual revenue is less than $100 million during the most recently completed fiscal year. We may continue to be a smaller reporting company if either (i) the market value of our common stock held by non-affiliates is less than $250 million or (ii) our annual revenue is less than $100 million during the most recently completed fiscal year and the market value of our common stock held by non-affiliates is less than $700 million. If we are a smaller reporting company at the time we cease to be an emerging growth company, we may continue to rely on exemptions from certain disclosure requirements that are available to smaller reporting companies. Specifically, similar to emerging growth companies, smaller reporting companies have reduced disclosure obligations regarding executive compensation.

Item 1A. Risk Factors.

Investing in our common stock involves a high degree of risk. You should carefully consider the risk factors below together with the information contained elsewhere in this Annual Report on Form 10-K, including Part II, Item 8 "Financial Statements and Supplementary Data" and Part II, Item 7. "Management's Discussion and Analysis of Financial Condition and Results of Operations," and in our other public filings in evaluating our business. Before you decide to invest in our common stock, you should consider carefully the risks described below, together with the other information contained in this Annual Report, including our financial statements and the related notes. We believe the risks described below are the risks that are material to us as of the date of this Annual Report. If any of the following risks actually occur, our business, financial condition, results of operations and future growth prospects could be materially and adversely affected. In these circumstances, the market price of our common stock could decline, and our stockholders may lose all or part of their investment.

Risks related to our financial position and need for additional capital

We have incurred significant losses in each year since inception. We expect to incur losses for the foreseeable future and may never achieve or maintain profitability.

Since our inception, we have incurred significant losses on an aggregate basis. Our net loss was $28.1 million, $15.5 million and $15.2 million for the years ended December 31, 2019, 2018 and 2017, respectively. Our accumulated deficit was $90.5 million as of December 31, 2019. We have not generated any revenue to date from sales of any drugs and have financed our operations principally through private placements of our preferred stock. We have devoted substantially all of our efforts to research and development. Our lead product candidate, APR-246, is in clinical development, and our other product candidates are in preclinical research. As a result, we expect that it will be several years, if ever, before we have any product candidates ready for commercialization. We expect to continue to incur

significant expenses and increasing operating losses for the foreseeable future. The net losses we incur may fluctuate significantly from quarter to quarter.

To become and remain profitable, we must develop, obtain approval for and eventually commercialize a drug or drugs with significant market potential, either on our own or with a collaborator. This will require us to be successful in a range of challenging activities, including completing preclinical studies and clinical trials of our product candidates, obtaining marketing approval for these product candidates, manufacturing, marketing and selling those drugs for which we may obtain marketing approval and establishing and managing any collaborations for the development, marketing and/or commercialization of our product candidates. We may never succeed in these activities and, even if we do, may never generate revenues that are significant or large enough to achieve profitability. If we do achieve profitability, we may not be able to sustain or increase profitability on a quarterly or annual basis. Our failure to become and remain profitable would decrease the value of our company and could impair our ability to raise capital, maintain our research and development efforts, expand our business and/or continue our operations. A decline in the value of our company could also cause our stockholders to lose all or part of their investment.

Even if we succeed in commercializing one or more of our product candidates, we will continue to incur substantial research and development and other expenditures to develop and market additional product candidates. We may encounter unforeseen expenses, difficulties, complications, delays and other unknown factors that may adversely affect our business. The size of our future net losses will depend, in part, on the rate of future growth of our expenses and our ability to generate revenue. Our prior losses and expected future losses have had and will continue to have an adverse effect on our stockholders' equity and working capital.

Our product candidates, if approved, may not achieve commercial success. Our commercial revenues, if any, will be derived from sales of drugs that we do not expect to be commercially available for many years, if at all. If we are unable to obtain product approvals or generate significant commercial revenues, our business will be materially harmed.

Our limited operating history may make it difficult for you to evaluate the success of our business to date and to assess our future viability. We have never generated revenues and may never be profitable.

We are an early-stage company. Aprea Therapeutics AB, or Aprea AB, was originally incorporated in 2002 and commenced operations in 2006. We were incorporated in May 2019. Our operations to date have been limited to organizing and staffing our company, business planning, raising capital, developing our lead product candidate, APR-246, identifying potential product candidates, conducting preclinical studies of our product candidates and conducting clinical trials of our product candidates. All of our product candidates other than APR-246 are in preclinical research. We have not yet demonstrated our ability to successfully complete large-scale, pivotal clinical trials, obtain marketing approvals, manufacture commercial-scale drug products or arrange for a third party to do so on our behalf, or conduct sales and marketing activities necessary for successful drug commercialization. Typically, it takes about six to ten years to develop a new drug from the time it is in Phase 1 clinical trials to when it is approved for treating patients, but in many cases it may take longer. Consequently, any predictions you make about our future success or viability may not be as accurate as they could be if we had a longer operating history.

In addition, as a business with a limited operating history, we may encounter unforeseen expenses, difficulties, complications, delays and other known and unknown factors. We may need to transition from a company with a research focus to a company capable of supporting commercial activities. We may not be successful in such a transition.

As we continue to build our business, we expect our financial condition and operating results may fluctuate significantly from quarter to quarter and year to year due to a variety of factors, many of which are beyond our control. Accordingly, you should not rely upon the results of any particular quarterly or annual periods as indications of future operating performance.

We will need substantial additional funding, which may not be available to us on acceptable terms or at all. If we are unable to raise capital when needed, we may be forced to delay, reduce and/or eliminate our research and drug development programs or future commercialization efforts.

Developing drug products, including conducting preclinical studies and clinical trials, is a very time-consuming, expensive and uncertain process that takes years to complete. We expect our expenses to increase in connection with our ongoing activities, particularly as we conduct clinical trials of, and seek marketing approval for, APR-246 and our other product candidates. In addition, if we obtain marketing approval for any of our product candidates, we expect to incur significant commercialization expenses related to drug sales, marketing, manufacturing and distribution to the extent that such sales, marketing, manufacturing and distribution are not the responsibility of any collaborator that we may have at such time for any such product candidate. Furthermore, since the completion of our IPO, we have incurred and expect to incur additional costs associated with operating as a public company. Accordingly, we will need to obtain substantial additional funding in connection with our continuing operations. If we are unable to raise capital when needed or on attractive terms, we may be forced to delay, reduce and/or eliminate our research and drug development programs or future commercialization efforts.

We believe that our existing cash and cash equivalents as of December 31, 2019 will enable us to fund our operating expenses and capital expenditure requirements into 2023. Our estimate as to how long we expect our existing cash and cash equivalents to be able to continue to fund our operations is based on assumptions that may prove to be wrong, and we could use our available capital resources sooner than we currently expect. Further, changing circumstances, some of which may be beyond our control, could cause us to consume capital significantly faster than we currently anticipate, and we may need to seek additional funds sooner than planned. Our future capital requirements will depend on many factors, including:

- the scope, progress, results and costs of our current and future clinical trials of APR-246 for our current targeted indications;
- the scope, progress, results and costs of drug discovery, preclinical research and clinical trials for APR-246 and our other product candidates;
- the number of future product candidates that we pursue and their development requirements;
- the costs, timing and outcome of regulatory review of our product candidates;
- the extent to which we acquire or invest in businesses, products and technologies, including entering into or maintaining licensing or collaboration arrangements for product candidates on favorable terms, although we currently have no commitments or agreements to complete any such transactions;
- the costs and timing of future commercialization activities, including drug sales, marketing, manufacturing and distribution, for any of our product candidates for which we receive marketing approval, to the extent that such sales, marketing, manufacturing and distribution are not the responsibility of any collaborator that we may have at such time;
- the amount of revenue, if any, received from commercial sales of our product candidates, should any of our product candidates receive marketing approval;
- the costs of preparing, filing and prosecuting patent applications, maintaining, defending and enforcing our intellectual property rights and defending intellectual property-related claims;
- our headcount growth and associated costs as we expand our business operations and our research and development activities; and
- the costs of operating as a public company.

Raising additional capital may cause dilution to our stockholders and restrict our operations or require us to relinquish rights to our product candidates.

We expect our expenses to increase in connection with our planned operations. Until such time, if ever, as we can generate substantial revenues from the sale of drugs, we expect to finance our cash needs through a combination of equity offerings, debt financings, collaborations, strategic alliances and/or licensing arrangements. To the extent that we raise additional capital through the sale of equity or convertible debt securities, ownership interests in our securities may be diluted, and the terms of these securities could include liquidation or other preferences and anti-dilution protections that could adversely affect the rights of our common stockholders. In addition, debt financing, if available, would result in fixed payment obligations and may involve agreements that include restrictive covenants that limit our ability to take specific actions, such as incurring additional debt, making capital expenditures, creating liens, redeeming stock or declaring dividends, that could adversely impact our ability to conduct our business. In addition, securing financing could require a substantial amount of time and attention from our management and may divert a disproportionate amount of their attention away from day-to-day activities, which may adversely affect our management's ability to oversee the development of our product candidates.

If we raise additional funds through collaborations, strategic alliances or licensing arrangements with third parties, we may have to relinquish valuable rights to our technology, future revenue streams or product candidates or grant licenses on terms that may not be favorable to us. If we are unable to raise additional funds when needed, we may be required to delay, reduce and/or eliminate our product candidate development or future commercialization efforts or grant rights to develop and market product candidates that we would otherwise prefer to develop and market ourselves.

Risks related to the discovery, development and commercialization of our product candidates

We are substantially dependent on the success of our lead product candidate, APR-246, which is currently in multiple clinical trials. Our clinical trials of APR-246 may not be successful. If we are unable to obtain approval for and commercialize APR-246 or experience significant delays in doing so, our business will be materially harmed.

Our future success is substantially dependent on our ability to timely obtain marketing approval for, and then successfully commercialize, APR-246, our lead product candidate. We are investing a majority of our efforts and financial resources in the research and development of APR-246. Our other product candidates are in earlier stages of development. Our business depends entirely on the successful development and commercialization of our product candidates. We currently have no drugs approved for sale and generate no revenues from sales of any products, and we may never be able to develop a marketable product.

APR-246 will require additional clinical development, evaluation of clinical, preclinical and manufacturing activities, marketing approval in multiple jurisdictions, substantial investment and significant marketing efforts before we generate any revenues from product sales. We are not permitted to market or promote APR-246, or any other product candidates, before we receive marketing approval from the FDA and comparable foreign regulatory authorities, and we may never receive such marketing approvals.

The success of APR-246 will depend on several factors, including the following:

- successful and timely completion of our ongoing clinical trials of APR-246;
- initiation and successful patient enrollment and completion of additional clinical trials on a timely basis;
- our ability to demonstrate APR-246's safety, tolerability and efficacy to the FDA or any comparable foreign regulatory authority for marketing approval;
- timely receipt of marketing approvals for APR-246;

- obtaining and maintaining patent protection, trade secret protection and regulatory exclusivity, both in the United States and internationally;
- successfully defending and enforcing our rights in our intellectual property portfolio;
- avoiding and successfully defending against any claims that we have infringed, misappropriated or otherwise violated any intellectual property of any third party;
- the performance of our future collaborators, if any;
- the extent of, and our ability to timely complete, any required post-marketing approval commitments imposed by FDA or other applicable regulatory authorities;
- establishment of supply arrangements with third-party raw materials and drug product suppliers and manufacturers who are able to manufacture clinical trial and commercial quantities of APR-246 drug substance and drug product and to develop, validate and maintain a commercially viable manufacturing process that is compliant with current good manufacturing practices, or cGMP, at a scale sufficient to meet anticipated demand and over time enable us to reduce our cost of manufacturing;
- establishment of scaled production arrangements with third-party manufacturers to obtain finished products that are compliant with cGMP and appropriately packaged for sale;
- 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;
- the availability of coverage and adequate reimbursement and pricing by third-party payors and government authorities;
- the availability, perceived advantages, relative cost, relative safety and relative efficacy of alternative and competing treatments; and
- our ability to compete with other therapies.

We do not have complete control over many of these factors, including certain aspects of clinical development and the regulatory submission process, potential threats to our intellectual property rights and the manufacturing, marketing, distribution and sales efforts of any future collaborator. Accordingly, we cannot assure you that we will ever be able to generate revenue through the sale of APR-246. If we are not successful in commercializing APR-246, or are significantly delayed in doing so, our business will be materially harmed.

We may find it difficult to enroll patients in our clinical trials given the relatively smaller patient population who have the diseases for which our product candidates are being developed. If we experience delays or difficulties in the enrollment of patients in clinical trials, our receipt of necessary marketing approvals could be delayed or prevented.

We 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 these trials as required by the FDA or comparable foreign regulatory authorities. Patient enrollment is a significant factor in the timing of clinical trials. In particular, because our clinical trials of APR-246 are focused on indications with relatively small patient populations, our ability to enroll eligible patients may be limited or may result in slower enrollment than we anticipate.

Patient enrollment may be affected if our competitors have ongoing clinical trials for product candidates that are under development for the same indications as our product candidates, and patients who would otherwise be eligible for our clinical trials instead enroll in clinical trials of our competitors' product candidates. Patient enrollment may also be affected by other factors, including:

- size and nature of the patient population;
- severity of the disease under investigation;
- availability and efficacy of approved drugs for the disease under investigation;
- patient eligibility criteria for the trial in question;
- patients' and clinicians' perceived risks and benefits of the product candidate under study;
- competing clinical trials;
- efforts to facilitate timely enrollment in clinical trials;
- patient referral practices of physicians;
- the ability to monitor patients adequately during and after treatment;
- proximity and availability of clinical trial sites for prospective patients; and
- continued enrollment of prospective patients by clinical trial sites.

Our inability to enroll a sufficient number of patients for our clinical trials would 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, which would cause the value of our company to decline and limit our ability to obtain additional financing.

The reactivation of p53 is a novel and unproven therapeutic approach and our development of APR-246 may never lead to a marketable product.

We are developing APR-246 for its ability to reactivate the tumor suppressor protein p53, the protein product of the *TP53* gene and the most commonly mutated gene in cancer. We are also developing a next-generation p53 reactivator, APR-548, for potential use in multiple hematologic malignancy indications. We believe that mutant p53 is an attractive target for novel cancer therapy due to the high incidence of p53 mutations across a range of cancer types and the universally inferior prognosis for cancer patients with mutated p53. However, to our knowledge, no one has advanced a product candidate with this mechanism of action into clinical development. The scientific evidence to support the feasibility of developing these product candidates is both preliminary and limited. For instance, even though APR-246 has shown promising results in preclinical studies and early-stage clinical trials, we may not succeed in demonstrating safety and efficacy of APR-246 in larger-scale clinical trials, including our pivotal Phase 3 clinical trial. Advancing APR-246 as a novel product to reactivate p53 creates significant challenges for us, including:

- obtaining marketing approval, as obtaining regulatory approval of a p53 reactivator from the FDA or comparable foreign regulatory authorities has never been done before;
- educating medical personnel regarding the potential efficacy and safety benefits, as well as the challenges, of incorporating our product candidates, if approved, into treatment regimens; and
- establishing the sales and marketing capabilities to gain market acceptance, if approved.

If serious adverse or unacceptable side effects are identified during the development of our product candidates or we observe limited efficacy of our product candidates, we may need to abandon or limit the development of one or more of our product candidates.

Adverse events or unacceptable side effects caused by, or other unexpected properties of, our product candidates could cause us, any future collaborators, an institutional review board, or IRB, or regulatory authorities to interrupt, delay or halt clinical trials of one or more of our product candidates and could result in the (i) delay or denial of marketing approval by the FDA or comparable foreign regulatory authorities, (ii) approval with significant restrictions on distribution or (iii) required labeling information regarding safety concerns, if approved.

In general, our clinical trials of APR-246 include cancer patients who are very sick and whose health is deteriorating, and we expect that additional clinical trials of APR-246 and our other product candidates will include similar patients with deteriorating health. Multiple patients in our trials have experienced adverse events, including serious adverse events. The most commonly reported adverse events include nausea, vomiting, constipation, dizziness and neutropenia. Some patients in our trials have experienced serious adverse events. In the Phase 3 MDS Trial, serious adverse events, regardless of causality, reported for more than one patient as of March 18, 2020 were: febrile neutropenia (21%), pyrexia (8%), lung infection (7%), muscle weakness (5%), confusional state (3%), pneumonia (3%), respiratory failure (3%), sepsis (3%), cellulitis (2%), acute febrile neutrophilic dermatosis (2%), acute kidney injury (2%), acute respiratory distress syndrome (2%), cardiac failure (2%), dyspnea (2%), encephalopathy (2%), hypotension (2%), hypoxia (2%), pericarditis (2%), thrombocytopenia (2%), pneumonitis (2%), urinary tract infection (2%). In the U.S. Phase 1b/2 MDS/AML Trial, serious adverse events, regardless of causality, reported for more than one patient as of March 18, 2020 were: febrile neutropenia (33%), pneumonia (20%), sepsis (11%), lung infection (9%), pyrexia (7%), dehydration (5%), muscle weakness (5%), respiratory failure (5%), vomiting (5%), angina (4%), atrial fibrillation (4%), embolism (4%), intracranial hemorrhage (4%), multi-organ failure (4%). In the French Phase 1b/2 MDS/AML Trial, serious adverse events, regardless of causality, reported for more than one patient as of March 18, 2020 were: Febrile neutropenia (30%), device related infection (9%), sepsis (8%), lung disorder (6%), ataxia (4%), cellulitis (4%), colitis (4%), dizziness (4%), large intestine infection (4%), lung infection (4%), pneumonia (4%), septic shock (4%), subdural hematoma (4%), urinary tract infection (4%). In the Phase 2 MDS/AML post-transplant trial there have been no serious adverse events, regardless of causality, reported in more than one patient as of March 18, 2020. In the Phase 1 AML Trial, serious adverse events, regardless of causality, reported for more than one patient as of March 18, 2020 were: febrile neutropenia (50%), sepsis (25%). In the Phase 1b/2 Clinical Trial of APR 246 in Platinum Sensitive Ovarian Cancer (PiSARRO), serious adverse events, regardless of causality, reported in more than one patient were: device related infection (17%), vomiting (17%), febrile neutropenia (8%), infection (6%), small intestinal obstruction (6%) and thrombocytopenia (6%).

Some patients have died during their participation in the clinical trials for APR-246; there have been two deaths reported by an investigator as possibly related to both APR-246 and azacitidine, one death reported by an investigator as possibly related to APR-246 and four deaths reported by an investigator as possibly related to azacitidine. We believe that the deaths with any relation to APR-246 may have been caused by the underlying disease, other comorbidities from which such patient was suffering or the other co-administered treatments. Any deaths occurring in our clinical trials, whether related to our product candidate or not, could affect perceptions relating to our product candidate.

If any of our product candidates are associated with adverse events or undesirable side effects or have properties that are unexpected, our trials could be suspended or terminated and the FDA or comparable foreign regulatory authorities could order us to cease further development of or deny approval of our product candidates for any or all targeted indications. We, or any future collaborators, may 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. Drug-related side effects could affect patient recruitment or the ability of enrolled patients to complete the trial or result in potential product liability claims. Any of these occurrences may harm our business, results of operations, financial condition and prospects significantly.

The outcome of preclinical testing and early clinical trials may not be predictive of the success of later clinical trials, interim results of a clinical trial do not necessarily predict final results, and the results of our clinical trials may not satisfy the requirements of the FDA or comparable foreign regulatory authorities.

We currently have no drugs approved for sale and we cannot guarantee that we will ever have marketable drugs. Clinical failure can occur at any stage of clinical development. Clinical trials may produce negative or inconclusive results, and we or any future collaborators may decide, or regulators may require us, to conduct additional clinical trials or preclinical studies. We will be required to demonstrate with substantial evidence through adequate and well-controlled clinical trials that our product candidates are safe and effective for use in treating specific conditions in order to obtain marketing approvals for their commercial sale. Success in preclinical studies and early-stage clinical trials does not mean that future larger registration clinical trials will be successful because product candidates in later-stage clinical trials may fail to demonstrate safety and efficacy to the satisfaction of the FDA and non-U.S. regulatory authorities despite having progressed through preclinical studies and early-stage clinical trials. Product candidates that have shown promising results in preclinical studies and early-stage clinical trials may still suffer significant setbacks in subsequent registration clinical trials. Additionally, the outcome of preclinical studies and early-stage clinical trials may not be predictive of the success of later-stage clinical trials.

From time to time, we may publish or report interim or preliminary data from our clinical trials. Interim or preliminary data from clinical trials that we may conduct may not be indicative of the final results of the trial and are subject to the risk that one or more of the clinical outcomes may materially change as patient enrollment continues and more patient data become available. Interim or preliminary data also remain subject to audit and verification procedures that may result in the final data being materially different from the interim or preliminary data. As a result, interim or preliminary data should be viewed with caution until the final data are available.

In addition, the design of a clinical trial can determine whether its results will support approval of a drug and flaws in the design of a clinical trial may not become apparent until the clinical trial is well advanced. We have limited experience in designing clinical trials and may be unable to design and conduct a clinical trial to support marketing approval. Further, if our product candidates are found to be unsafe or lack efficacy, we will not be able to obtain marketing approval for them and our business would be harmed. A number of companies in the pharmaceutical industry, including those with greater resources and experience than us, have suffered significant setbacks in advanced clinical trials, even after obtaining promising results in preclinical studies and earlier clinical trials.

In some instances, there can be significant variability in safety and efficacy results between different clinical trials of the same product candidate due to numerous factors, including changes in trial protocols, differences in size and type of the patient populations, differences in and adherence to the dosing regimen and other trial protocols and the rate of dropout among clinical trial participants. We do not know whether any clinical trials we may conduct will demonstrate consistent or adequate efficacy and safety sufficient to obtain marketing approval to market our product candidates.

We have multiple clinical trials of APR-246 currently ongoing. In the event that an adverse safety issue, clinical hold or other adverse finding occurs in one or more of our clinical trials of APR-246, such event could adversely affect our other clinical trials of APR-246. Moreover, there is a relatively limited safety data set for product candidates that are designed to reactivate p53. An adverse safety issue or other adverse finding in a clinical trial conducted by a third party with a product candidate reactivate p53, could adversely affect our clinical trials of APR-246.

Further, our product candidates may not be approved even if they achieve their primary endpoints in Phase 3 clinical trials or registration trials. The FDA or comparable foreign regulatory authorities may disagree with our trial design and our interpretation of data from preclinical studies and clinical trials. In addition, any of these regulatory authorities may change requirements for the approval of a product candidate even after reviewing and providing comments or advice on a protocol for a pivotal clinical trial that has the potential to result in approval by the FDA or comparable foreign regulatory authorities. In addition, any of these regulatory authorities may also approve a product candidate for fewer or more limited indications than we request or may grant approval contingent on the performance of costly post-marketing clinical trials. In addition, the FDA or other comparable foreign regulatory authorities may not approve the labeling claims that we believe would be necessary or desirable for the successful commercialization of our product candidates.

Before obtaining marketing approvals for the commercial sale of any product candidate for a target indication, we must demonstrate with substantial evidence gathered in preclinical studies and adequate and well-controlled clinical trials, and, with respect to approval in the United States, to the satisfaction of the FDA and elsewhere to the satisfaction of other comparable foreign regulatory authorities, that the product candidate is safe and effective for use for that target indication. There is no assurance that the FDA or other comparable foreign regulatory authorities will consider our future clinical trials to be sufficient to serve as the basis for approval of one of our product candidates for any indication. The FDA and other comparable foreign regulatory authorities retain broad discretion in evaluating the results of our clinical trials and in determining whether the results demonstrate that a product candidate is safe and effective. If we are required to conduct additional clinical trials of a product candidate than we expect prior to its approval, we will need substantial additional funds and there is no assurance that the results of any such additional clinical trials will be sufficient for approval.

Clinical drug development is a lengthy and expensive process, with an uncertain outcome. If clinical trials of our product candidates fail to demonstrate safety and efficacy to the satisfaction of regulatory authorities or do not otherwise produce positive results, we may incur additional costs, experience delays in completing, or ultimately be unable to complete, the development of our product candidates or be unable to obtain marketing approval.

Before obtaining marketing approval from regulatory authorities for the sale of our product candidates, we must complete preclinical development and then conduct extensive clinical trials to demonstrate the safety and efficacy of our product candidates. Clinical testing is expensive, difficult to design and implement, can take many years to complete and is uncertain as to outcome. A failure of one or more clinical trials can occur at any stage of testing. The outcome of preclinical studies and early-stage clinical trials may not be predictive of the success of later clinical trials, and interim results of a clinical trial, such as the results of our ongoing clinical trials of APR-246, do not necessarily predict final results. Moreover, preclinical and clinical data are often susceptible to varying interpretations and analyses, and many companies that have believed their product candidates performed satisfactorily in preclinical studies and clinical trials have nonetheless failed to obtain marketing approval of their drugs.

We do not know whether ongoing clinical trials will be completed on schedule or at all, or whether future clinical trials will begin on time, need to be redesigned, enroll patients on time or be completed on schedule, if at all. Clinical trials can be delayed for a variety of reasons, including delays related to:

- obtaining regulatory authorization to commence a trial;
- reaching agreement on acceptable terms with prospective contract research organizations, or CROs, and clinical trial sites, the terms of which can be subject to extensive negotiation and may vary significantly among different CROs and clinical trial sites;
- obtaining institutional review board or ethics committee approval at each clinical trial site;
- recruiting suitable patients to participate in a trial;
- developing and validating any companion diagnostic to be used in the trial, to the extent we are required to do so;
- patients failing to comply with the clinical trial protocol or dropping out of a trial;
- clinical trial sites failing to comply with the clinical trial protocol or dropping out of a trial;
- addressing any conflicts with new or existing laws or regulations;
- the need to add new clinical trial sites;
- manufacturing sufficient quantities of product candidate for use in clinical trials and ensuring clinical trial material is provided to clinical sites in a timely manner; or

- obtaining advice from regulatory authorities regarding the statistical analysis plan to be used to evaluate the clinical trial data or other trial design issues.

We may experience numerous unforeseen events during, or as a result of, clinical trials that could delay or prevent our ability to receive marketing approval or commercialize our product candidates, including:

- we may receive feedback from regulatory authorities that requires us to modify the design of our clinical trials;
- clinical trials of our product candidates may produce negative or inconclusive results, and we may decide, or regulators may require us, to conduct additional clinical trials or abandon drug development programs;
- the number of patients required for clinical trials of our product candidates may be larger than we anticipate, enrollment in these clinical trials may be slower than we anticipate or participants may drop out of these clinical trials at a higher rate than we anticipate;
- our third-party contractors, including our CROs, may fail to comply with regulatory requirements or meet their contractual obligations to us in a timely manner, or at all;
- we, our investigators, or any of the overseeing IRBs or ethics committees might decide to suspend or terminate clinical trials of our product candidates for various reasons, including non-compliance with regulatory requirements, a finding that our product candidates have undesirable side effects or other unexpected characteristics, or a finding that the participants are being exposed to unacceptable health risks;
- the cost of clinical trials of our product candidates may be greater than we anticipate;
- the supply or quality of our product candidates or other materials necessary to conduct clinical trials of our product candidates may be insufficient or inadequate;
- regulators may revise the requirements for approving our product candidates, or such requirements may not be as we anticipate; and
- any future collaborators that conduct clinical trials may face any of the above issues, and may conduct clinical trials in ways they view as advantageous to them but that are suboptimal for us.

If we are required to conduct additional clinical trials or other testing of our product candidates beyond those that we currently contemplate, if we are unable to successfully complete clinical trials of our product candidates or other testing, if the results of these trials or tests are not positive or are insufficiently positive to support marketing approval, or if there are safety concerns, we may:

- incur unplanned costs;
- be delayed in obtaining marketing approval for our product candidates or not obtain marketing approval at all;
- obtain marketing approval in some countries and not in others;
- obtain marketing approval for indications or patient populations that are narrower or more limited in scope than intended or desired;
- obtain marketing approval subject to significant use or distribution restrictions or with labeling that includes significant safety warnings, including boxed warnings;
- be subject to additional post-marketing testing requirements; or

· have the drug removed from the market after obtaining marketing approval.

Our drug development costs will also increase if we experience delays in testing or marketing approvals. We do not know whether clinical trials will begin as planned, will need to be restructured or will be completed on schedule, or at all. Furthermore, we rely on third-party CROs and clinical trial sites to ensure the proper and timely conduct of our clinical trials, and while we have agreements governing their committed activities, we have limited influence over their actual performance. 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 drugs to market before we do and impair our ability to successfully commercialize our product candidates and may harm our business and results of operations.

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 focus on research programs and product candidates that we identify for specific indications. As a result, we may forego or delay pursuit of opportunities with other product candidates or for other indications that later prove to have greater commercial potential. Our resource allocation decisions may cause us to fail to capitalize on viable commercial drugs 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 drugs. 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 strategic arrangements in cases in which it would have been more advantageous for us to retain sole development and commercialization rights to such product candidate.

The failure to obtain required regulatory clearances or approvals for any companion diagnostic tests that we may pursue may prevent or delay approval of any of our product candidates. Moreover, the commercial success of any of our product candidates that require a companion diagnostic will be tied to the receipt of any required regulatory clearances or approvals and the continued availability of such tests.

In connection with the clinical development of our product candidates for certain indications, we may work with collaborators to develop or obtain access to companion diagnostic tests to identify appropriate patients for our product candidates. We may rely on third parties for the development, testing and manufacturing of these companion diagnostics, the application for and receipt of any required regulatory clearances or approvals, and the commercial supply of these companion diagnostics. The FDA and foreign regulatory authorities regulate companion diagnostics as medical devices that will likely be subject to clinical trials in conjunction with the clinical trials for product candidates, and which will require separate regulatory clearance or approval prior to commercialization. This process could include additional meetings with health authorities, such as a pre-submission meeting and the requirement to submit an investigational device exemption. In the case of a companion diagnostic that is designated as “significant risk device,” approval of an investigational device exemption by the FDA and IRB is required before such diagnostic is used in conjunction with the clinical trials for a corresponding product candidate. We or our third-party collaborators may fail to obtain the required regulatory clearances or approvals, which could prevent or delay approval of our product candidates. In addition, the commercial success of any of our product candidates that require a companion diagnostic will be tied to and dependent upon the receipt of required regulatory clearances or approvals and the continued ability of such third parties to make the companion diagnostic commercially available to us on reasonable terms in the relevant geographies.

We may not be successful in our efforts to identify or discover additional potential product candidates.

Our research programs may initially show promise in identifying potential product candidates, yet fail to yield product candidates for clinical development for a number of reasons, including:

· the research methodology used may not be successful in identifying potential product candidates;

- potential product candidates may, on further study, be shown to have harmful side effects or other characteristics that indicate that they are unlikely to be drugs that will receive marketing approval and/or achieve market acceptance; and

- potential product candidates may not be safe or effective in treating their targeted diseases.

Research programs to identify new product candidates require substantial technical, financial and human resources. If we are unable to identify suitable compounds for preclinical and clinical development, our business would be harmed.

If any of our product candidates receives marketing approval and we, or others, later discover that the drug is less effective than previously believed or causes undesirable side effects that were not previously identified, our ability, or that of any future collaborators, to market the drug could be compromised.

Clinical trials of our product candidates must be conducted in carefully defined subsets of patients who have agreed to enter into clinical trials. Consequently, it is possible that our clinical trials, or those of any future collaborator, 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 one or more of our product candidates receives marketing approval and we, or others, discover that the drug is less effective than previously believed or causes undesirable side effects that were not previously identified, a number of potentially significant negative consequences could result, including:

- regulatory authorities may withdraw their approval of the drug or seize the drug;

- we, or any future collaborators, may be required to recall the drug, change the way the drug is administered or conduct additional clinical trials;

- additional restrictions may be imposed on the marketing of, or the manufacturing processes for, the particular drug;

- we may be subject to fines, injunctions or the imposition of civil or criminal penalties;

- regulatory authorities may require the addition of labeling statements, such as a “black box” warning or a contraindication;

- we, or any future collaborators, may be required to create a Medication Guide outlining the risks of the previously unidentified side effects for distribution to patients;

- we, or any future collaborators, could be sued and held liable for harm caused to patients;

- the drug may become less competitive in the marketplace; and

- our reputation may suffer.

Any of these events could have a material and adverse effect on our operations and business and could adversely impact our stock price.

Even if any of our product candidates receive marketing approval, they may fail to achieve the degree of market acceptance by physicians, patients, healthcare payors and others in the medical community necessary for commercial success.

If any of our product candidates receive marketing approval, they may nonetheless fail to gain sufficient market acceptance by physicians, patients, healthcare payors and others in the medical community. For example, current cancer treatments like chemotherapy and radiation therapy are well-established in the medical community, and doctors may continue to rely on these treatments. If our product candidates do not achieve an adequate level of acceptance, we may

not generate significant revenues from sales of drugs 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 potential advantages of the product compared to alternative therapies;
- the prevalence and severity of any side effects;
- whether the product is designated under physician and other provider treatment guidelines as a first-, second- or third-line therapy;
- our ability, or the ability of any future collaborators, to offer the product for sale at competitive prices;
- the product's convenience and ease of administration for patients and healthcare practitioners 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 and safety information contained in the product's approved labeling;
- the strength of sales, marketing and distribution support;
- changes in the standard of care for the targeted indications for the product; and
- the availability of coverage by, and the amount of reimbursement from, government payors, managed care plans and other third-party payors.

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

The pharmaceutical and biotechnology industries generally, and the cancer drug sector specifically, are highly competitive and characterized by rapidly advancing technologies, evolving understanding of disease etiology and a strong emphasis on proprietary drugs. We face competition with respect to APR-246, our lead product candidate, and will face competition with respect to any product candidates that we may seek to discover and develop or commercialize in the future, from major pharmaceutical, specialty pharmaceutical and biotechnology companies. There are a number of major pharmaceutical, specialty pharmaceutical and biotechnology companies that currently market and sell drugs or are pursuing the development of drugs for the treatment of cancer. Potential competitors also include academic institutions and governmental agencies and public and private research institutions.

There are a large number of companies developing or marketing treatments for cancer, including the indications for which we may develop product candidates. Many of the companies that we compete or may compete against in the future have significantly greater financial resources and expertise in research and development, manufacturing, preclinical testing, conducting clinical trials, obtaining regulatory approvals and marketing approved drugs than we do. Small or early-stage companies may also prove to be significant competitors, particularly through collaborative arrangements with large and established companies. These competitors also compete with us in recruiting and retaining qualified scientific and management personnel and establishing clinical trial sites and patient registration for clinical trials, as well as in acquiring technologies complementary to, or that may be necessary for, our programs.

Our commercial opportunity could be reduced or eliminated if our competitors develop and commercialize drugs that are safer, more effective, have fewer or less severe side effects, are more convenient or are less expensive than any drugs that we may develop. Our competitors also may obtain FDA or other comparable foreign regulatory approval for their

drugs more rapidly than we may obtain approval for ours, which could result in our competitors establishing a strong market position before we are able to enter the market. The key competitive factors affecting the success of all of our product candidates, if approved, are likely to be their efficacy, safety, convenience, price, the effectiveness of companion diagnostics in guiding the use of related therapeutics, the level of generic competition and the availability of reimbursement from government and other third-party payors.

The most common methods of treating patients with cancer are surgery, radiation and drug therapy. There are a variety of available drug therapies marketed for cancer. In many cases, these drugs are administered in combination to enhance efficacy. Some of the currently-approved drug therapies are branded and subject to patent protection and may be established as the standard of care for treatment of indications for which we may choose to seek regulatory approvals. Many of these approved drugs are well-established therapies and are widely accepted by physicians, patients and third-party payors, and, even if our product candidates were to be approved, there can be no assurance that our product candidates would displace existing treatments. In addition to currently marketed therapies, there are also a number of drugs in late-stage clinical development to treat cancer, including the indications for which we are developing product candidates. These clinical-stage product candidates may provide efficacy, safety, convenience and other benefits that are not provided by currently-marketed therapies. As a result, they may provide significant competition for any of our product candidates for which we obtain regulatory approval.

We are developing our lead product candidate, APR-246, to reactivate p53 for the treatment of various cancers. We are aware of other product candidates that are in clinical development for the treatment of various cancers through the reactivation of p53. Although there is a subset of drugs that directly target the p53 pathway, there are many cancer drugs that claim to affect the p53 pathway by upstream or complementary pathways. We are aware of selective small molecule inhibitors that are designed to target the p53-MDM2 interaction in various stages of clinical development being tested by F. Hoffmann-La Roche Ltd and Hoffmann-La Roche Inc., or collectively Roche, Amgen Inc., Novartis AG, Daiichi Sankyo Co., Ltd, and Aileron Therapeutics, Inc. If APR-246 were to be approved for the indications for which we currently have ongoing clinical trials, it will compete with currently-marketed drugs or drugs that may be approved for marketing by the FDA or comparable foreign regulatory authorities in the future and such competition will not be limited to drugs that act through the reactivation of p53.

Our business and operations would suffer in the event of IT system failures, cybersecurity attacks, data breaches, or vulnerabilities in our or our third-party vendors' information security program or defenses.

Our business relies upon information technology systems operated by us and by our third party service providers. These systems may fail or experience operational disruption, experience cybersecurity attacks, or be damaged by computer viruses and unauthorized access. In the ordinary course of business, we collect, store and transmit confidential information (including but not limited to intellectual property, proprietary business information and personal information). It is critical that we do so in a secure manner to maintain the confidentiality and integrity of such confidential information. While we are currently in the process of developing and implementing policies and procedures to ensure the security and integrity of our information technology systems and confidential and proprietary information, we do not currently have any such policies and procedures formally in place. If we fail to develop and maintain adequate policies and procedures for the protection of our information technology systems and confidential and proprietary information, we may be vulnerable to security breaches or disruptions and system breakdowns or other damage or interruptions, and face legal and reputational risk. We also have outsourced elements of our operations to third parties, and as a result we manage a number of third-party vendors and other contractors and consultants who have access to or store our confidential information. We do not conduct audits or formal evaluations of our third-party vendors' information technology systems and cannot be sure that our third-party vendors have sufficient measures in place to ensure the security and integrity of their information technology systems and our confidential and proprietary information. If our third-party vendors fail to protect their information technology systems and our confidential and proprietary information, we may be vulnerable to disruptions in service and unauthorized access to our confidential or proprietary information and we could incur liability and reputational damage and the further development and commercialization of our product candidates could be delayed. While we have not, to our knowledge, experienced any material IT system failures or cybersecurity attacks to date, we frequently must defend against and respond to cybersecurity incidents and attacks and cannot assure you that our data protection efforts and our investment in information technology will prevent significant breakdowns, data leakages, compromises of personal information or

confidential commercial information, other operationally significant breaches in our systems or those of our third-party vendors and other contractors and consultants, or other cyber incidents that could have a material adverse effect upon our reputation, business, operations or financial condition. If such an event were to occur and cause interruptions in our operations, it could result in a material disruption of our development programs, business operations, a breach of sensitive personal information or a loss or corruption of critical data assets including trade secrets or other proprietary information. For example, the loss of clinical trial data from future clinical trials could result in delays in our regulatory approval efforts and significantly increase our costs to recover or reproduce the data. Such IT system failures, cybersecurity attacks or vulnerabilities to our or our third-party vendors' information security programs or defenses could result in legal liability, reputational damage, business interruption, and our competitive position could be harmed and the further development and commercialization of our products or any future products could be delayed or disrupted. Moreover, containing and remediating any IT system failure, cybersecurity attack or vulnerability may require significant investment of resources. Furthermore, significant security breaches or disruptions of our internal information technology systems or those of our third-party vendors and other contractors and consultants could result in the loss, misappropriation and/or unauthorized access, use, or disclosure of, or the prevention of access to, confidential information (including trade secrets or other intellectual property, proprietary business information and personal information), which could result in financial, legal, business and reputational harm to us.

If we are required to in the future and if we are unable to successfully develop companion diagnostic tests for our product candidates that require such tests, or experience significant delays in doing so, we may not realize the full commercial potential of these product candidates.

We may be required by the FDA to develop, either by ourselves or with collaborators, companion diagnostic tests for our product candidates for certain indications. To be successful, we or our collaborators will need to address a number of scientific, technical, regulatory and logistical challenges. We have no prior experience with medical device or diagnostic test development. If we choose to develop and seek FDA approval for companion diagnostic tests on our own, we will require additional personnel. We may rely on third parties for the design, development and manufacture of companion diagnostic tests for our therapeutic product candidates that require such tests. If these parties are unable to successfully develop companion diagnostics for these therapeutic product candidates, or experience delays in doing so, we may be unable to enroll enough patients for our current and planned clinical trials, the development of these therapeutic product candidates may be adversely affected, these therapeutic product candidates may not obtain marketing approval, and we may not realize the full commercial potential of any of these therapeutics that obtain marketing approval. Any failure to successfully develop this companion diagnostic may cause or contribute to delayed enrollment of this trial, and may prevent us from initiating or completing further clinical trials to support marketing approval for our product candidates. As a result, our business, results of operations and financial condition could be materially harmed.

If, in the future, we are unable to establish sales and marketing capabilities or enter into agreements with third parties to sell and market our product candidates, we may not be successful in commercializing our product candidates if and when they are approved.

We do not have a sales or marketing infrastructure and have no experience in the sale or marketing of pharmaceutical drugs. We are not currently a party to a strategic collaboration that provides us with access to a collaborator's resources in selling or marketing drugs. To achieve commercial success for any approved drug for which sales and marketing is not the responsibility of any strategic collaborator that we may have in the future, we must either develop a sales and marketing organization or outsource these functions to other third parties. In the future, we may choose to build a sales and marketing infrastructure to market or co-promote some of our product candidates if and when they are approved, or enter into collaborations with respect to the sale and marketing of our product candidates.

There are risks involved with both establishing our own sales and marketing capabilities and entering into arrangements with third parties to perform these services. For example, recruiting and training a sales force is expensive and time-consuming and could delay any commercial launch of a product candidate. If the commercial launch of a product candidate for which we recruit a sales force and establish marketing capabilities is delayed or does not occur for any reason, we would have prematurely or unnecessarily incurred these commercialization expenses. This may be costly, and our investment would be lost if we cannot retain or reposition our sales and marketing personnel.

Factors that may inhibit our efforts to commercialize our product candidates on our own include:

- our inability to recruit and retain adequate numbers of effective sales and marketing personnel;
- limitations or restrictions on the ability of sales personnel to appropriately market the product to physicians or other healthcare professionals;
- the lack of complementary drugs to be offered by sales personnel, which may put us at a competitive disadvantage relative to companies with more extensive product lines;
- unforeseen costs and expenses associated with creating an independent sales and marketing organization; and
- inability to obtain sufficient coverage and reimbursement from third-party payors and governmental agencies.

If we enter into arrangements with third parties to perform sales and marketing services, our revenues from the sale of drugs or the profitability of these revenues to us are likely to be lower than if we were to market and sell any drugs that we develop ourselves. In addition, we may not be successful in entering into arrangements with third parties to sell and market our product candidates or may be unable to do so on terms that are favorable to us. We likely will have little control over such third parties, and any of them may fail to devote the necessary resources and attention to sell and market our product candidates effectively. If we do not establish sales and marketing capabilities successfully, either on our own or in collaboration with third parties, we will not be successful in commercializing our product candidates.

If the FDA or comparable foreign regulatory authorities approve generic versions of any of our product candidates that receive marketing approval, or such authorities do not grant our product candidates appropriate periods of data or market exclusivity before approving generic versions of our product candidates, the sales of our product candidates could be adversely affected.

Once an NDA is approved, the drug covered thereby becomes a “reference-listed drug” in the FDA’s publication, “Approved Drug Products with Therapeutic Equivalence Evaluations.” Manufacturers may seek marketing approval of generic versions of reference-listed drugs through submission of abbreviated new drug applications, or ANDAs, in the United States. In support of an ANDA, a generic manufacturer need not conduct clinical trials demonstrating safety and efficacy. Rather, the applicant generally must show that its drug is pharmaceutically equivalent to the reference listed drug, in that it has the same active ingredient(s), dosage form, strength, route of administration and conditions of use or labeling as the reference-listed drug, and that the generic version is bioequivalent to the reference-listed drug, meaning it is absorbed in the body at the same rate and to the same extent. Generic drugs may be significantly less costly to bring to market than the reference-listed drug and companies that produce generic drugs are generally able to offer them at lower prices. Thus, following the introduction of a generic drug, a significant percentage of the sales of any branded product or reference-listed drug is typically lost to the generic drug.

The FDA may not approve an ANDA for a generic drug until any applicable period of non-patent exclusivity for the reference-listed drug has expired. The Federal Food, Drug, and Cosmetic Act, or FDCA, provides a period of five years of non-patent exclusivity for a new drug containing a new chemical entity, or NCE. During the exclusivity period, the FDA may not accept for review an ANDA or a 505(b)(2) NDA submitted by another company for another version of such product candidate where the applicant does not own or have a legal right of reference to all the data required for approval. However, an application may be submitted after four years if it contains a certification of patent invalidity or non-infringement. The FDCA also provides three years of marketing exclusivity for an NDA, 505(b)(2) NDA or supplement to an approved NDA if new clinical investigations, other than bioavailability studies, that were conducted or sponsored by the applicant are deemed by the FDA to be essential to the approval of the application, for example, for new indications, dosages or strengths of an existing product candidate. This three-year exclusivity covers only the conditions associated with the new clinical investigations and does not prohibit the FDA from approving ANDAs for product candidates containing the original active agent. Five-year and three-year exclusivity will not delay the submission or approval of a full NDA. However, an applicant submitting a full NDA would be required to conduct or obtain a right of reference to all of the nonclinical studies and adequate and well-controlled clinical trials necessary to

demonstrate safety and effectiveness. Manufacturers may seek to launch these generic drugs following the expiration of the marketing exclusivity period, even if we still have patent protection for our drug.

Competition that our product candidates may face from generic versions of our product candidates could materially and adversely impact our future revenue, profitability and cash flows and substantially limit our ability to obtain a return on the investments we have made in those product candidates. Our future revenues, profitability and cash flows could also be materially and adversely affected and our ability to obtain a return on the investments we have made in those product candidates may be substantially limited if our product candidates, if and when approved, are not afforded the appropriate periods of non-patent exclusivity.

Even if we obtain regulatory approval of any product candidate, the approved product may be subject to post-approval studies and will remain subject to ongoing regulatory requirements. If we fail to comply, or if concerns are identified in subsequent studies, our approval could be withdrawn, and our product sales could be suspended.

If we are successful at obtaining regulatory approval for APR-246 or any of our other product candidates, regulatory agencies in the United States and other countries where a product will be sold may require extensive additional clinical trials or post-approval clinical trials that are expensive and time-consuming to conduct. These trials may reveal side effects or other harmful effects in patients that use our products after they are on the market, which may result in the limitation or withdrawal of our drugs from the market. Alternatively, we may not be able to conduct such additional trials, which might force us to abandon our efforts to develop or commercialize certain product candidates. Even if post-approval studies are not requested or required, after our products are approved and on the market, there might be safety issues that emerge over time that require a change in product labeling, additional postmarket studies or clinical trials, imposition of distribution and use restrictions under a Risk Evaluation and Mitigation Strategy, or REMS, or withdrawal of the product from the market, which would cause our revenue to decline.

Additionally, any products that we may successfully develop will be subject to ongoing regulatory requirements after they are approved. These requirements will govern the manufacturing, packaging, marketing, distribution, and use of our products. If we fail to comply with such regulatory requirements, approval for our products may be withdrawn, and product sales may be suspended. We may not be able to regain compliance, or we may only be able to regain compliance after a lengthy delay, significant expense, lost revenues and damage to our reputation.

Even if we are able to commercialize any product candidate, such product candidate may become subject to unfavorable pricing regulations, third-party coverage and reimbursement policies or healthcare reform initiatives, which could harm our business.

The regulations that govern marketing approval, pricing, coverage and reimbursement for new drugs 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 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 might obtain marketing approval for a product in a particular country, but then be subject to price regulations that delay our commercial launch of the product, possibly for lengthy time periods, and 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 investment in one or more product candidates, even if our product candidates obtain marketing approval.

Our ability to commercialize any products successfully also will depend in part on the extent to which reimbursement and coverage for these products and related treatments will be available from government authorities, private health insurers and other organizations, and if reimbursement and coverage is available, the level of reimbursement and coverage. Government authorities and third-party payors, such as private health insurers and health maintenance organizations, decide which medications they will pay for and establish reimbursement levels. A primary trend in the healthcare industry in the United States and elsewhere is cost containment. Government authorities and third-party payors have attempted to control costs by limiting coverage and the amount of reimbursement for particular medications. Increasingly, the third-party payors who reimburse patients or healthcare providers, such as government and private insurance plans, are requiring that drug companies provide them with predetermined discounts from list prices, and are seeking to reduce the prices charged or the amounts reimbursed for medical products. We cannot be sure that coverage

and reimbursement will be available for any drug that we commercialize and, if coverage and reimbursement are available, we cannot be sure as to the level of reimbursement. Reimbursement may impact the demand for, or the price of, any product candidate for which we obtain marketing approval. If reimbursement is not available or is available only to limited levels, we may not be able to successfully commercialize any product candidate for which we obtain marketing approval.

There may be significant delays in obtaining reimbursement for newly approved drugs, and coverage may be more limited than the purposes 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 reimbursed in all cases or at a rate that covers our costs, including research, development, manufacture, sale and distribution. Interim reimbursement levels for new drugs, if applicable, may also not be sufficient to cover our costs and may not be made permanent. Reimbursement rates may vary according to the use of the drug and the clinical setting in which it is used, may be based on reimbursement levels already set for lower cost drugs, may be incorporated into existing payments for other items or services and may reflect budgetary constraints or imperfections in Medicare data. Net prices for drugs may be reduced by mandatory discounts or rebates required by government healthcare programs or private payors and by any future relaxation of laws that presently restrict imports of drugs from countries where they may be sold at lower prices than in the United States. Third-party payors often rely upon Medicare coverage policy and payment limitations in setting their own reimbursement rates. Our inability to promptly obtain coverage and adequate reimbursement rates from both government-funded and private payors for new products that we develop and for which we obtain marketing approval could have a material adverse effect on our operating results, our ability to raise capital needed to commercialize products and our overall financial condition.

Product liability lawsuits against us could cause us to incur substantial liabilities and to limit commercialization of any drugs that we may develop. Our insurance policies may be inadequate and may potentially expose us to unrecoverable risk.

We face an inherent risk of product liability exposure related to the testing of our product candidates in clinical trials and will face an even greater risk if we commercially sell any drugs that we may develop. If we cannot successfully defend ourselves against claims that our product candidates or drugs caused injuries, we will incur substantial liabilities. Regardless of merit or eventual outcome, liability claims may result in:

- decreased demand for any product candidates or drugs that we may develop;
- injury to our reputation and significant negative media attention;
- withdrawal of clinical trial participants;
- significant costs to defend the related litigation;
- substantial monetary awards to trial participants or patients;
- loss of revenue;
- reduced resources of our management to pursue our business strategy; and
- the inability to commercialize any drugs that we may develop.

We currently hold clinical trial liability insurance coverage for up to $3.0 million, but that coverage may not be adequate to cover any and all liabilities that we may incur. We would need to increase our insurance coverage when we begin the commercialization of our product candidates, if ever. Insurance coverage is increasingly expensive. We may not be able to maintain insurance coverage at a reasonable cost or in an amount adequate to satisfy any liability that may arise.

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

In some countries, particularly member states of the EU, the pricing of prescription pharmaceuticals is subject to governmental control. In these countries, pricing negotiations with governmental authorities can take considerable time after the receipt of marketing approval for a product. In addition, there can be considerable pressure by governments and other stakeholders on prices and reimbursement levels, including as part of cost containment measures. 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 distribution, or arbitrage between low-priced and high-priced member states, can further reduce prices. In some countries, we, or our future collaborators, may be required to conduct a clinical trial or other studies that compare the cost-effectiveness of our product candidates to other available therapies in order to obtain or maintain reimbursement or pricing approval. Publication of discounts by third-party payors or authorities may lead to further pressure on the prices or reimbursement levels within the country of publication and other countries. If reimbursement of any product candidate approved for marketing is unavailable or limited in scope or amount, or if pricing is set at unsatisfactory levels, our business could be materially harmed.

An epidemic or pandemic disease outbreak, including the recent coronavirus (COVID-19), could disrupt our business operations as well as the business or operations of our single third-party manufacturer, our CROs, clinical data management organizations, medical institutions and clinical investigators, or other third parties with whom we conduct business which may have a material adverse effect on our business, results of operations, financial condition and prospects.

An epidemic or pandemic disease outbreak, including the recent 2019 novel coronavirus *(COVID-19),* could severely disrupt our operations or the operations of third parties that we depend on, including our single third-party contract manufacturer, our CROs, clinical data management organizations, medical institutions and clinical investigators, and have a material adverse effect on our business, results of operations, financial condition and prospects. In addition, supply chain disruptions due to response to *COVID-19* or otherwise could have a material adverse effect on the availability or cost of materials for the API for APR-246. Quarantines, restrictions or bans in travel into and within the countries in which we operate, our manufacturer produces the API for APR-246 or where we conduct our clinical trials could impede, delay, limit or prevent the production or delivery or release of our product candidates to our trial sites, and trial investigators, patients or other critical staff could be restricted from traveling to our trial sites. In addition, some of our clinical sites could slow or cease patient recruitment, patient treatment and/or access to patient data. We have observed a recent decrease in both patient screening and patient enrollment as a result of the *COVID-19* pandemic. Any or all of these factors could impede, delay, limit or prevent completion of our ongoing clinical trials, and ultimately lead to the delay or denial of regulatory approval of our product candidates, which would materially adversely affect our business, results of operations, financial conditions and prospects.

While there is significant uncertainty relating to the potential effect of the coronavirus on our business and operations, infections may become more widespread and travel restrictions may worsen, including in the United States, Sweden and other countries where our trials are conducted or the API for APR-246 is manufactured, any of which could have a material adverse effect our business, results of operations, financial conditions and prospects. There could be potential effect of the coronavirus to the business at FDA, the EMA and other regulators, which could result in delays of reviews and approvals of our product candidate or our proposed clinical trials.

Risks related to our dependence on third parties

We rely on third parties to conduct our clinical trials and some aspects of our research and preclinical studies, and those third parties may not perform satisfactorily, including failing to meet deadlines for the completion of such trials, research and studies.

We currently rely on third parties, such as CROs, clinical data management organizations, medical institutions and clinical investigators, to conduct our clinical trials of APR-246 and expect to continue to rely upon third parties to conduct additional clinical trials of APR-246 and our other product candidates. We currently rely and expect to continue

to rely on third parties to conduct some aspects of our research and preclinical studies. Any of these third parties may terminate their engagements with us at any time. If we need to enter into alternative arrangements, it would delay our drug development activities.

Our reliance on these third parties for research and development activities will reduce our control over these activities but will not relieve us of our regulatory responsibilities. For example, we will remain responsible for ensuring that each of our clinical trials is conducted in accordance with the general investigational plan, study protocols for the trial, statistical analysis plan and other study-specific documents (for example, monitoring and blinding plans). Moreover, the FDA requires us to comply with standards, commonly referred to as Good Clinical Practice, or GCP, International Council for Harmonization of Technical Requirements for Pharmaceuticals for Human Use, or ICH, guidelines, and regulations regarding the informed consent process, safety reporting requirements, data collection guidelines, and other regulations for conducting, recording and reporting the results of clinical trials to assure that data and reported results are credible and accurate and that the rights, integrity and confidentiality of trial participants are protected. The EMA, also requires us to comply with similar standards. Regulatory authorities enforce these GCP requirements through periodic inspections of trial sponsors, principal investigators and trial sites. If we or any of our CROs fail to comply with applicable GCP requirements, the clinical data generated in our clinical trials may be deemed unreliable and the FDA, EMA or comparable foreign regulatory authorities may require us to perform additional clinical trials before approving our marketing applications. We cannot assure you that upon inspection by a given regulatory authority, such regulatory authority will determine that any of our clinical trials comply with GCP and other applicable regulations. In addition, our clinical trials must be conducted with product produced under current Good Manufacturing Practices, or cGMP, regulations. Our failure to comply with these regulations may require us to conduct new clinical trials, which would delay the marketing approval process. We also are required to register certain ongoing clinical trials and post the results of certain completed clinical trials on a government-sponsored database, ClinicalTrials.gov, within certain timeframes. Failure to do so can result in fines, adverse publicity and civil and criminal sanctions.

Furthermore, these third parties may also have relationships with other entities, some of which may be our competitors. If these third parties do not successfully carry out their contractual duties, meet expected deadlines or conduct our clinical trials in accordance with regulatory requirements or our stated protocols, we will not be able to obtain, or may be delayed in obtaining, marketing approvals for our product candidates and will not be able to, or may be delayed in our efforts to, successfully commercialize our product candidates.

We also expect to rely on other third parties to store and distribute drug supplies for our clinical trials. Any performance failure on the part of such third parties could delay clinical development or marketing approval of our product candidates or commercialization of our product candidates, producing additional losses and depriving us of potential revenue from sales of drugs.

We are currently dependent on a single third party manufacturer for the manufacture of the active pharmaceutical ingredient for APR-246. This reliance on a single third party increases the risk that we will not have sufficient quantities of our product candidates or drugs or such quantities at an acceptable cost, which could delay, prevent or impair our development or commercialization efforts.

We do not have any manufacturing facilities or personnel, and we currently have no plans to build our own clinical or commercial scale manufacturing capabilities. We currently contract with third parties for the manufacture of our product candidates for certain preclinical trials and clinical trial materials, including raw materials and consumables necessary for their manufacture, consistent with applicable cGMP requirements. We intend to continue to contract for these materials in the future, including commercial manufacture if our product candidates receive marketing approval.

The API, for APR-246 is currently manufactured by a single contract manufacturer. Although we may do so in the future, we do not currently have arrangements in place for redundant supply of the API for APR-246. We contract with a different manufacturer for formulation of drug product, sterile fill of vials, labeling and packaging, and the storage and distribution of APR-246 to clinical sites.

We expect to rely on third-party manufacturers or third-party collaborators for the manufacture of our product candidates for commercial supply of any of our product candidates for which we or any of our future collaborators obtain marketing

approval. We may be unable to establish any agreements with third-party manufacturers or to do so on acceptable terms. Even if we are able to establish agreements with third-party manufacturers, reliance on third-party manufacturers entails additional risks, including:

- the possible failure of the third party to manufacture our product candidate according to our schedule, or at all, including if our third-party contractors give greater priority to the supply of other products over our product candidates or otherwise do not satisfactorily perform according to the terms of the agreements between us and them;
- the possible termination or nonrenewal of agreements by our third-party contractors at a time that is costly or inconvenient for us;
- the possible breach by the third-party contractors of our agreements with them;
- the failure of third-party contractors to comply with applicable regulatory requirements;
- the possible failure of the third party to manufacture our product candidates according to our specifications;
- the possible mislabeling of clinical supplies, potentially resulting in issues including 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.

The facilities used by our contract manufacturers to manufacture our product candidates must be approved by the FDA or the EMA pursuant to inspections that will be conducted after we submit our NDA to the FDA or our MAA to the EMA. We do not have complete control over all aspects of the manufacturing process of, and are dependent on, our contract manufacturing partners for compliance with cGMP regulations for manufacturing both active drug substances and finished drug products. Third-party manufacturers may not be able to comply with cGMP regulations or similar regulatory requirements outside of the United States. If our contract manufacturers cannot successfully manufacture material that conforms to our specifications and the strict regulatory requirements of the FDA or comparable foreign regulatory bodies, they will not be able to secure and/or maintain marketing approval for their manufacturing facilities. In addition, we do not have complete control over the ability of our contract manufacturers to maintain adequate quality control, quality assurance and qualified personnel. If the FDA, the EMA or a comparable foreign regulatory authority does not approve these facilities for the manufacture of our product candidates or if it withdraws any such approval in the future, we may need to find alternative manufacturing facilities, which would significantly impact our ability to develop, obtain marketing approval for or market our product candidates, if approved.

Our failure, or the failure of our third-party manufacturers, to comply with applicable regulations could result in sanctions being imposed on us, including fines, injunctions, civil penalties, delays, suspension or withdrawal of approvals, license revocation, seizures or recalls of product candidates or drugs, operating restrictions and criminal prosecutions, any of which could significantly and adversely affect supplies of our product candidates and harm our business and results of operations.

Any drugs that we may develop may compete with other product candidates and drugs for access to manufacturing facilities. There are a limited number of manufacturers that operate under cGMP regulations and that might be capable of manufacturing for us.

Any performance failure on the part of our existing or future manufacturers could delay clinical development or marketing approval.

We do not currently have arrangements in place for redundant supply of the API of APR-246. If our current contract manufacturer cannot perform as agreed, we may be required to replace that manufacturer. Although we believe that there are several potential alternative manufacturers who could manufacture our product candidates, we may incur added costs and delays in identifying and qualifying any such replacement.

Our current and anticipated future dependence upon others for the manufacture of our product candidates or drugs may adversely affect our future profit margins and our ability to commercialize any drugs that receive marketing approval on a timely and competitive basis.

Although we currently plan to retain all commercial rights to APR-246 and our product candidates, we may enter into strategic collaborations for the development, marketing and commercialization of APR-246 and our other product candidates. If those collaborations are not successful, the development, marketing and/or commercialization of our product candidates that are the subject of such collaborations would be harmed.

As we further develop APR-246, we may build a commercial infrastructure with the capability to directly market it to a variety of markets and geographies. Although we currently plan to retain all commercial rights to APR-246 and our product candidates, we may enter into strategic collaborations for the development, marketing and commercialization of APR-246 and our other product candidates. Our likely collaborators for any collaboration arrangements include large and mid-size pharmaceutical companies, regional and national pharmaceutical companies and biotechnology companies. If we do enter into any such arrangements with any third parties, we will likely have limited control over the amount and timing of resources that our collaborators dedicate to the development, marketing and/or commercialization of our product candidates. Our ability to generate revenues from these arrangements will depend on our collaborators' abilities to successfully perform the functions assigned to them in these arrangements. In addition, any future collaborators may have the right to abandon research or development projects and terminate applicable agreements, including funding obligations, prior to or upon the expiration of the agreed upon terms.

Collaborations involving our product candidates would pose the following risks to us:

- collaborators have significant discretion in determining the efforts and resources that they will apply to these collaborations;
- collaborators may not perform their obligations as expected;
- collaborators may not pursue development, marketing and/or commercialization of our product candidates or may elect not to continue or renew development, marketing or commercialization programs based on clinical trial results, changes in the collaborator's strategic focus or available funding or external factors such as an acquisition that diverts resources or creates competing priorities;
- collaborators may delay clinical trials, provide insufficient funding for a clinical trial program, stop a clinical trial or abandon a product candidate, repeat or conduct new clinical trials or require a new formulation of a product candidate for clinical testing;
- collaborators could independently develop, or develop with third parties, drugs that compete directly or indirectly with our product candidates or product candidates;
- a collaborator with marketing and distribution rights to one or more drugs may not commit sufficient resources to the marketing and distribution of such drug or drugs;
- disagreements with collaborators, including disagreements over proprietary rights, contract interpretation or the preferred course of development, might cause delays or termination of the research, development or commercialization of product candidates, might lead to additional responsibilities for us with respect to product candidates, or might result in litigation or arbitration, any of which would be time-consuming and expensive;

- collaborators may not properly obtain, maintain, defend and enforce our intellectual property rights or may use our proprietary information in such a way as to invite litigation that could jeopardize or invalidate our proprietary information or expose us to potential litigation;

- collaborators may infringe, misappropriate or otherwise violate the intellectual property rights of third parties, which may expose us to litigation and potential liability;

- we may lose certain valuable rights under circumstances identified in any collaboration arrangement that we enter into, such as if we undergo a change of control;

- collaborations may be terminated and, if terminated, may result in a need for additional capital to pursue further development, marketing and/or commercialization of the applicable product candidates;

- collaborators may learn about our discoveries, data, proprietary information, trade secrets, or compounds and use this knowledge to compete with us in the future; and

- the number and type of our collaborations could adversely affect our attractiveness to future collaborators or acquirers.

Collaboration agreements may not lead to development or commercialization of product candidates in the most efficient manner, or at all.

Risks related to our intellectual property

If we are unable to obtain and maintain intellectual property protection for APR-246 or any other product candidates we develop or for our technology, our competitors could develop and commercialize products or technology similar or identical to ours, and our ability to successfully commercialize APR-246 or any product candidates we may develop, and our technology may be adversely affected.

Our commercial success will depend in large part on obtaining and maintaining patent, trademark and trade secret protection of our proprietary technologies and our product candidates, which include APR-246 and others, their respective components, formulations, methods used to manufacture them and methods of treatment, as well as successfully defending these patents against third-party challenges. We seek to protect our proprietary position by filing patent applications in the United States and abroad relating to our product candidates as well as other technologies that are important to our business. Our ability to stop unauthorized third parties from making, using, selling, offering to sell or importing our product candidates is dependent upon the extent to which we have rights under valid and enforceable patents or trade secrets that cover these activities.

The chemical structure of APR-246 is in the public domain. Accordingly, we do not own or license any composition of matter patents claiming the compound of APR-246 and will not in the future own or license any composition of matter patents claiming the chemical structure of APR-246 as described in the public domain. Our patent portfolio for APR-246 currently consists of method-of-use and formulation patent claims, and dosing, manufacturing processes, crystalline solid form, and combination therapy patent application claims. Our existing patents and any future patents we obtain may not be sufficiently broad to prevent others from using our technology or from developing competing products and technologies. Any failure to obtain or maintain patent protection with respect to APR-246 and our other product candidates could have a material adverse effect on our business, financial condition, results of operations and growth prospects. If it is later determined that our activities or product candidates infringe, misappropriate or otherwise violate the intellectual property of third parties we may be liable for damages, enhanced damages or subjected to an injunction, any of which could have a material adverse effect on our business.

The patenting process is expensive and time-consuming, and we may not be able to file and prosecute all necessary or desirable patent applications at a reasonable cost or in a timely manner. In addition, we may not pursue or obtain patent protection in all relevant markets. During the course of business we have decided not to pursue certain products or

processes and have not pursued certain corresponding intellectual property. However, we may decide to pursue such products or processes again in the future. It is also possible that we will fail to identify patentable aspects of our research and development output before it is too late to obtain patent protection.

The patent position of pharmaceutical and biotechnology companies generally is highly uncertain and involves complex legal and factual questions for which many legal principles remain unresolved. In recent years patent rights have been the subject of significant litigation. As a result, the issuance, scope, validity, enforceability and commercial value of our patent rights are highly uncertain. Our pending and future patent applications may not result in patents being issued in the United States or in other jurisdictions which protect our technology or products or which effectively prevent others from commercializing competitive technologies and products.

Our ability to obtain and maintain valid and enforceable patents depends on whether the differences between our inventions and the prior art, including our own previously filed patent applications and scientific publications, allow our inventions to be patentable over the prior art. We are aware of certain scientific publications by our inventors and other third parties that disclose subject matter, including the composition of APR-246, relating to certain of our patents, that may be used by third parties to challenge the validity and enforceability of our patents and patent applications. If such third parties are successful, we could lose valuable patent rights. In the United States, an inventor's own publication cannot be used as prior art to the inventor's patent application on the same subject matter when published less than one year before the effective filing date of the patent application. Such a publication may be considered prior art in certain jurisdictions that do not provide such a grace period. Publications of discoveries in the scientific literature often lag behind the actual discoveries, and patent applications in the United States and other jurisdictions are typically not published until 18 months after filing, or in some cases not at all. Therefore, we cannot be certain that we were the first to make the inventions claimed in our patents or pending patent applications, or that we were the first to file for patent protection of such inventions. In addition, the U.S. Patent and Trademark Office, or USPTO, might require that the term of a patent issuing from a pending patent application be disclaimed and limited to the term of another patent that is commonly owned or names a common inventor. Although we enter into non-disclosure and confidentiality agreements with parties who have access to confidential or patentable aspects of our research and development output, such as our employees, corporate collaborators, outside scientific collaborators, CROs, contract manufacturers, consultants, advisors, and other third parties, certain of these parties have and others may in the future breach the agreements and disclose such output before a patent application is filed, thereby jeopardizing our ability to seek patent protection.

Moreover, the coverage claimed in a patent application can be significantly reduced before the patent is issued, and its scope can be reinterpreted after issuance. Even if our patent applications issue as patents, they may not issue in a form that will provide us with any meaningful protection, prevent competitors from competing with us or otherwise provide us with any competitive advantage. Our competitors may be able to circumvent our patents by developing similar or alternative technologies or products in a non-infringing manner.

The issuance of a patent is not conclusive as to its inventorship, scope, validity or enforceability, and our patents may be challenged in the courts or patent offices in the United States and abroad. Such challenges may result in the patent claims of our patents being narrowed, invalidated or held unenforceable, which could limit our ability to stop or prevent us from stopping others from using or commercializing similar or identical technology and products, or limit the duration of the patent protection of our technology and products. In addition, some of our owned patents and patent applications may in the future be co-owned with third parties. If we do not have exclusive control of the grant of licenses under any such third-party co-owners' interest in such patents or patent applications or we are otherwise unable to secure such exclusive rights, such co-owners may be able to license their rights to other third parties, including our competitors, and our competitors could market competing products and technology. In addition, we may need the cooperation of any such co-owners of our co-owned patents in order to enforce such patents against third parties, and such cooperation may not be provided to us.

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 patent portfolio may not provide us with sufficient rights to exclude others from commercializing products similar or identical to ours or otherwise provide us with a competitive advantage. Upon the expiration of our current patents, we may lose the right to exclude others from practicing these inventions, including APR-246 based on patent exclusivity.

The expiration of these patents could also have a similar material adverse effect on our business, results of operations, financial condition and prospects.

Our proprietary position for APR-246 depends upon patents that consist of method-of-use and formulation patent claims, which may not prevent a competitor or other third party from using the same product candidate for another use or in another formulation.

Composition-of-matter patent claims on the active pharmaceutical ingredient, or API, in pharmaceutical drug products are generally considered to be the favored form of intellectual property protection for drug products because such patents may provide protection without regard to any particular method of use or manufacture or formulation of the API used. The chemical structure of APR-246 is in the public domain. Accordingly, we do not own or license any composition of matter patents claiming the compound of APR-246 and will not in the future own or license any composition of matter patents claiming the chemical structure of APR-246 as described in the public domain.

Method-of-use patent claims protect the use of a product for the specified method and dosing or formulation patent claims cover dosing regimens or formulations of the API. These types of patent claims do not prevent a competitor or other third party from marketing an identical API for an indication that is outside the scope of the method claims or from developing a different dosing regimen or formulation that is outside the scope of the dosing or formulation claims. Moreover, with respect to method-of-use patents, even if competitors or other third parties do not actively promote their product for our targeted indications or uses for which we may obtain patents, physicians may recommend that patients use these products off-label, or patients may do so themselves. Although off-label use may infringe or contribute to the infringement of method-of-use patents, the practice is common and such infringement is difficult to prevent or prosecute. In addition, there are numerous publications and other prior art that may be relevant to our patents and may be used to challenge the validity of such patents in litigation or other intellectual property-related proceedings. If such challenges are successful, our patents may be narrowed or found to be invalid and we may lose valuable intellectual property rights. Any of the foregoing could have a material adverse effect on our business, financial conditions and results of operations and prospects.

Issued patents covering our product candidates and other technologies could be narrowed or found invalid or unenforceable if challenged in court or before administrative bodies in the United States or abroad.

If we seek to enforce a patent covering our product candidates or other technologies against a third party, that third party could assert that such patent is invalid or unenforceable. In patent litigation in the United States, challenges to validity or enforceability are commonplace. Grounds for a validity challenge could be an alleged failure to meet any of several statutory requirements, including lack of patentable subject matter, lack of novelty, obviousness, inadequate written description, indefiniteness, or lack of enablement. Grounds for an unenforceability assertion could be an allegation that relevant information was withheld from or a misleading statement was made to the USPTO during prosecution.

In addition, third parties may raise claims challenging the validity or enforceability of our patents before administrative bodies in the United States or abroad, even outside the context of litigation. Such mechanisms include preissuance submission of prior art to the USPTO and re-examination, post-grant review, *inter partes* review, interference proceedings, derivation proceedings, and equivalent proceedings in foreign jurisdictions (*e.g.*, opposition proceedings). Moreover, we may have to participate in interference proceedings declared by the USPTO to determine priority of invention or in post-grant challenge proceedings, such as oppositions in a foreign patent office, that challenge our priority of invention or other features of patentability with respect to our patents and patent applications. An adverse determination in any such submission, proceeding or litigation could reduce the scope of, or invalidate or render unenforceable, our patent rights, allow third parties to commercialize our product candidates or other technologies and compete directly with us, without payment to us.

In the United States, an inventor’s own publication may not be effective prior art to the inventor’s patent application on the same subject matter when published less than one year before the effective filing date of the patent application. Such a publication might be considered prior art in certain jurisdictions that do not provide such a grace period. For those non-US jurisdictions, reliance on non-patent exclusivity may provide sufficient competitive protection to exclude others from commercializing generic versions of our products.

Such proceedings also may result in substantial cost and require significant time from our scientists and management, even if the eventual outcome is favorable to us. If we are unsuccessful in any such proceeding or other priority or inventorship dispute, we may be required to obtain and maintain licenses from third parties, including parties involved in any such interference proceedings or other priority or inventorship disputes. Such licenses may not be available on commercially reasonable terms or at all, or may be non-exclusive. If we are unable to obtain and maintain such licenses, we may need to cease the development, manufacture, and commercialization of one or more of the product candidates we may develop. The loss of exclusivity or the narrowing of our patent claims could limit our ability to stop others from using or commercializing similar or identical technology and products. Any of the foregoing could have a material adverse effect on our business, results of operations, financial condition and prospects.

We may be subject to other claims challenging the inventorship of our patents and other intellectual property.

We may also be subject to claims that former employees, collaborators or other third parties have an interest in our patents, trade secrets, or other intellectual property as an inventor or co-inventor. For example, we may have inventorship disputes arise from conflicting obligations of employees, consultants or others who are involved in developing our product candidates or other technologies. Litigation may be necessary to defend against these and other claims challenging inventorship of our patents, trade secrets or other intellectual property. If we fail in defending any such claims, in addition to paying monetary damages, we may lose valuable intellectual property rights, such as exclusive ownership of, or right to use, intellectual property that is important to our product candidates and other technologies. Even if we are successful in defending against such claims, litigation could result in substantial costs and be a distraction to management and other employees. Any of the foregoing could have a material adverse effect on our business, financial condition, results of operations and growth prospects.

If we do not obtain patent term extension or data exclusivity for any product candidates we may develop, our business may be materially harmed.

Depending upon the timing, duration and specifics of any FDA marketing approval of any product candidates we may develop, one or more of our U.S. patents may be eligible for limited patent term extension under the Drug Price Competition and Patent Term Restoration Act of 1984, commonly referred to as the Hatch-Waxman Act. The Hatch-Waxman Act permits a patent term extension of up to five years as compensation for patent term lost during the FDA regulatory review process. A patent term extension cannot extend the remaining term of a patent beyond a total of 14 years from the date of product approval, only one patent may be extended and only those claims covering the approved drug, a method for using it, or a method for manufacturing it may be extended. Similar extensions as compensation for patent term lost during regulatory review processes are also available in certain foreign countries and territories, such as in Europe under a Supplementary Patent Certificate. However, we may not be granted an extension in the United States and/or foreign countries and territories because of, for example, failing to exercise due diligence during the testing phase or regulatory review process, failing to apply within applicable deadlines, failing to apply prior to expiration of relevant patents, or otherwise failing to satisfy applicable requirements. Moreover, the applicable time period or the scope of patent protection afforded could be less than we request. If we are unable to obtain patent term extension or the term of any such extension is shorter than what we request, our competitors may obtain approval of competing products following our patent expiration, and our business, financial condition, results of operations and growth prospects could be materially harmed.

We may not be successful in obtaining, through acquisitions, in-licenses or otherwise, rights that may be necessary to our product candidates or other technologies.

The growth of our business may depend in part on our future ability to acquire or in-license any relevant third-party proprietary rights that we may identify as necessary or important to our business operations. For example, our programs may involve additional product candidates that may require the use of additional proprietary rights held by third parties. Our product candidates may also require specific formulations to work effectively and efficiently. These formulations may be covered by intellectual property rights held by others. We may develop products containing our compounds and pre-existing pharmaceutical compounds. These pharmaceutical compounds may be covered by intellectual property rights held by others. We may be required by the FDA or comparable foreign regulatory authorities to provide a companion diagnostic test or tests with our product candidates. These diagnostic test or tests may be covered by

intellectual property rights held by others. We may be unable to acquire or in-license such third-party intellectual property rights. We may fail to obtain any of these licenses at a reasonable cost or on reasonable terms, if at all, which would harm our business. We may need to cease use of the compositions or methods covered by such third-party intellectual property rights, and may need to seek to develop alternative approaches that do not infringe, misappropriate or otherwise violate intellectual property rights which may entail additional costs and development delays, even if we were able to develop such alternatives, which may not be feasible. Even if we are able to obtain a license to such intellectual property rights, any such license may be non-exclusive, which may allow our competitors access to the same technologies licensed to us.

Additionally, we sometimes collaborate with academic institutions and clinical research organizations to accelerate our research or development, including our research or development of APR-246, under written agreements with these institutions and organizations. In certain cases, these institutions and organizations may own or jointly own with us inventions that are created under such collaborations and provide us with an option to negotiate a license to any of the institution's rights in such inventions. Regardless of such option, we may be unable to negotiate a license within the specified timeframe or under terms that are acceptable to us. If we are unable to do so, the institution or organization may offer the intellectual property rights to others, potentially blocking our ability to pursue our program and allowing third parties to compete with us.

The licensing and acquisition of third-party intellectual property rights is a competitive practice, and companies that may be more established, or have greater resources than we do, may also be pursuing strategies to license or acquire third-party intellectual property rights that we may consider necessary or attractive in order to commercialize our product candidates. More established companies may have a competitive advantage over us due to their larger size and cash resources or greater clinical development and commercialization capabilities. In addition, companies that perceive us to be a competitor may be unwilling to assign or license rights to us. We also may be unable to license or acquire third-party intellectual property rights on terms that would allow us to make an appropriate return on our investment or at all. There can be no assurance that we will be able to successfully complete such negotiations and ultimately acquire the rights to the intellectual property surrounding the additional product candidates that we may seek to acquire. If we are unable to successfully obtain rights to third-party intellectual property that may be necessary, we may have to abandon development of such program and our business, results of operations, financial condition and prospects could suffer.

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

Recent or future patent reform legislation could increase the uncertainties and costs surrounding the prosecution of our patent applications and the enforcement or defense of our issued patents. Assuming that other requirements for patentability are met, prior to March 2013, in the United States, the first to invent the claimed invention was entitled to the patent, while outside the United States, the first to file a patent application was entitled to the patent regardless of whether another inventor had made the invention earlier. In March 2013, under the Leahy-Smith America Invents Act, or America Invents Act, the United States moved from a "first-to-invent" to a "first-to-file" system. Under a "first-to-file" system, assuming the other requirements for patentability are met, the first inventor to file a patent application generally will be entitled to a patent on the invention regardless of whether another inventor had made the invention earlier. A third party that files a patent application in the USPTO after March 2013, but before us, could therefore be awarded a patent covering an invention of ours even if we had made the invention before it was made by such third party. Since patent applications in the United States and most other countries are confidential for a period of time after filing or until issuance, we cannot be certain that we were the first to either (i) file any patent application related to our product candidates or other technologies or (ii) invent any of the inventions claimed in our patents or patent applications.

The America Invents Act includes a number of other significant changes to U.S. patent law, including provisions that affect the way patent applications are prosecuted, redefine prior art and establish a new post-grant review system. These include allowing third party submission of prior art to the USPTO during patent prosecution and additional procedures to attack the validity of a patent by USPTO-administered post-grant proceedings, including post-grant review, *inter partes* review, and derivation proceedings. Because of a lower evidentiary standard in USPTO proceedings compared to the evidentiary standard in United States federal courts necessary to invalidate a patent claim, a third party could potentially provide evidence in a USPTO proceeding sufficient for the USPTO to hold a claim invalid even though the same

evidence would be insufficient to invalidate the claim if first presented in a district court action. Accordingly, a third party may attempt to use the USPTO procedures to invalidate our patent claims that would not have been invalidated if first challenged by the third party in a district court action. An adverse determination in any such proceeding could reduce the scope of, or invalidate, our patent rights, allow third parties to commercialize our technology or products and compete directly with us, without payment to us, or result in our inability to manufacture or commercialize products without infringing third-party patent rights, all of which could have a material adverse effect on our business and financial condition. Accordingly, the America Invents Act and its implementation could increase the uncertainties and costs surrounding the prosecution of our patent applications and the enforcement or defense of our issued patents.

In addition, the patent positions of companies in the development and commercialization of biologics and pharmaceuticals are particularly uncertain. Recent U.S. Supreme Court rulings have narrowed the scope of patent protection available in certain circumstances and weakened the rights of patent owners in certain situations. This combination of events has created uncertainty with respect to the validity and enforceability of patents, once obtained. Depending on future actions by the U.S. Congress, the federal courts, and the USPTO, the laws and regulations governing patents could change in unpredictable ways that could have a material adverse effect on our existing patent portfolio and our ability to protect and enforce our intellectual property in the future.

We may become involved in lawsuits to protect or enforce our patents and other intellectual property rights, which could be expensive, time consuming and unsuccessful.

Competitors may infringe our patents, or we may be required to defend against claims of infringement. In addition, our patents also may become involved in inventorship, priority, validity or unenforceability disputes. To counter or defend against such claims can be expensive and time consuming. We may not prevail in any lawsuits that we initiate, and the damages or other remedies awarded, if any, may not be commercially meaningful. For example, in an infringement proceeding, a court may decide that a patent owned by us is invalid or unenforceable. There is also the risk that, even if the validity of these patents is upheld, the court will refuse to stop the third party on the ground that such third party's activities do not infringe our owned patents, including finding that the other party's use of our patented technology falls under the safe harbor to patent infringement under 35 U.S.C. § 271(e)(1). Even if resolved in our favor, these lawsuits are expensive and would consume time and other resources, including distracting our personnel from their normal responsibilities. In addition, there could be public announcements of the results of hearings, motions, or other interim proceedings or developments, and if securities analysts or investors perceive these results to be negative, it could have a substantial adverse effect on the price of our common stock. Such litigation or proceedings could substantially increase our operating losses and reduce the resources available for development activities or any future sales, marketing, or distribution activities. We may not have sufficient financial or other resources to conduct such litigation or proceedings adequately. Some of our competitors may be able to sustain the costs of such litigation or proceedings more effectively than we can because of their greater financial resources and more mature and developed intellectual property portfolios. Uncertainties resulting from the initiation and continuation of patent litigation or other proceedings could have a material adverse effect on our ability to compete in the marketplace. Furthermore, because of the substantial amount of discovery required in connection with intellectual property litigation, there is a risk that some of our confidential information could be compromised by disclosure during this type of litigation.

We may not be able to detect infringement against our patents which may be more difficult for formulation patents. Even if we detect infringement by a third party of our patents, we may choose not to pursue litigation against or settlement with the third party. If we later sue such third party for patent infringement, the third party may have certain legal defenses available to it, which otherwise would not be available except for the delay between when the infringement was first detected and when the suit was brought. Such legal defenses may make it impossible for us to enforce our patents against such third party.

If another party questions the patentability of any of our claims in our U.S. patents, the third party can request that the USPTO review the patent claims such as in an *inter partes* review, *ex parte* re-exam or post-grant review proceedings. These proceedings are expensive and may result in a loss of scope of some claims or a loss of the entire patent. In addition to potential USPTO review proceedings, we may become a party to patent opposition proceedings in the European Patent Office, or EPO, or similar proceedings in other foreign patent offices, where either our foreign patents are challenged. The costs of these opposition or similar proceedings could be substantial, and may result in a loss of

scope of some claims or a loss of the entire patent. An unfavorable result at the USPTO, EPO or other patent office may result in the loss of our right to exclude others from practicing one or more of our inventions in the relevant country or jurisdiction, which could have a material adverse effect on our business.

If we are sued for infringing, misappropriating or otherwise violating patents or other intellectual property rights of third parties, it will be costly and time consuming, and an unfavorable outcome in that litigation would have a material adverse effect on our business.

Our commercial success depends upon our ability to develop, manufacture, market and sell our product candidates and use our proprietary technologies without infringing, misappropriating or otherwise violating the intellectual property rights of third parties. There is a substantial amount of litigation involving patents and other intellectual property rights in the biotechnology and pharmaceutical industries. We may be exposed to, or threatened with, future litigation by third parties having patent or other intellectual property rights alleging that our product candidates and/or proprietary technologies infringe, misappropriate or otherwise violate their intellectual property rights. We cannot guarantee that our product candidates and other technologies that we have developed, are developing or may develop in the future will not infringe existing or future patents owned by third parties. U.S. and foreign issued patents and pending patent applications, which are owned by third parties, exist in the fields relating to our product candidates. As the biotechnology and pharmaceutical industries expand and more patents are issued, the risk increases that others may assert our product candidates infringe the patent rights of others. Moreover, it is not always clear to industry participants, including us, which patents cover various types of drugs, products or their methods of use or manufacture. Thus, because of the large number of patents issued and patent applications filed in our fields, there may be a risk that third parties may allege they have patent rights encompassing our product candidates, technologies or methods. It is also possible that patents owned by third parties of which we are aware, but which we do not believe are relevant to our product candidates or other technologies, could be found to be infringed by our product candidates or other technologies. In addition, because some patent applications in the United States may be maintained in secrecy until the patents are issued, patent applications in the United States and many foreign jurisdictions are typically not published until 18 months after filing, and publications in the scientific literature often lag behind actual discoveries, we cannot be certain that others have not filed patent applications covering our product candidates or technology. If any such patent applications issue as patents, and if such patents have priority over our patent applications or patents, we may be required to obtain rights to such patents owned by third parties which may not be available on commercially reasonable terms or at all, or may only be available on a non-exclusive basis.

If a third party claims that we infringe its intellectual property rights, we may face a number of issues even if we believe such claims are without merit, including, but not limited to:

- infringement and other intellectual property claims which, regardless of merit, may be expensive and time-consuming to litigate, may divert our management’s attention from our core business and may impact our reputation;
- substantial damages for infringement, which we may have to pay if a court decides that the product candidate or technology at issue infringes on or violates the third party’s rights, and, if the court finds that the infringement was willful, we could be ordered to pay treble damages and the patent owner’s attorneys’ fees;
- a court prohibiting us from developing, manufacturing, marketing or selling our product candidates, including APR-246, or from using our proprietary technologies, unless the third party licenses its patent rights to us, which it is not required to do;
- if a license is available from a third party, we may have to pay substantial royalties, upfront fees and other amounts, and/or grant cross-licenses to intellectual property rights for our product candidates or such license is only available on a non-exclusive basis; and
- redesigning our product candidates or processes so they do not infringe, which may not be possible or may require substantial monetary expenditures and time.

Some of our competitors may be able to sustain the costs of complex patent litigation more effectively than we can because they have substantially greater resources. In addition, any uncertainties resulting from the initiation and continuation of any litigation could have a material adverse effect on our ability to raise the funds necessary to continue our operations or could otherwise have a material adverse effect on our business, results of operations, financial condition and prospects. The occurrence of any of the foregoing could have a material adverse effect on our business, financial condition, results of operations or growth prospects.

We may choose to challenge the patentability of claims in a third party's U.S. patent by requesting that the USPTO review the patent claims in an *ex-parte* re-exam, *inter partes* review or post-grant review proceedings. These proceedings are expensive and may consume our time or other resources. We may choose to challenge a third party's patent in patent opposition proceedings in the EPO, or other foreign patent office. The costs of these opposition proceedings could be substantial, and may consume our time or other resources. If we fail to obtain a favorable result at the USPTO, EPO or other patent office then we may be exposed to litigation by a third party alleging that the patent may be infringed by our product candidates or proprietary technologies.

We may not be able to protect our intellectual property rights with patents throughout the world.

Filing, prosecuting and defending patents on all of our product candidates throughout the world would be prohibitively expensive, and the laws of some foreign countries may not protect our rights to the same extent as the laws of the United States. Competitors may use our technology in jurisdictions where we have not obtained patent protection to develop their own products and, further, may export otherwise infringing products to territories where we have patent protection but where enforcement is not as strong as in the United States. These products may compete with our product candidates in jurisdictions where we do not have any issued patents and our patent claims or other intellectual property rights may not be effective or sufficient to prevent them from so competing. Many companies have encountered significant problems in protecting and defending intellectual property rights in foreign jurisdictions. The legal systems of certain countries, particularly certain developing countries, do not favor the enforcement of patents and other intellectual property protection, particularly those relating to biopharmaceuticals, which could make it difficult for us to stop the infringement of our patents or marketing of competing products against third parties in violation of our proprietary rights generally. The initiation of proceedings to enforce our intellectual property rights or proceedings by third parties to challenge the scope or validity of our patent rights in foreign jurisdictions could result in substantial cost and divert our efforts and attention from other aspects of our business and could put our patents at risk of being invalidated or interpreted narrowly.

Many countries have compulsory licensing laws under which a patent owner may be compelled to grant licenses to third parties. In addition, many countries limit the enforceability of patents against government agencies or government contractors. In these countries, the patent owner may have limited remedies, which could materially diminish the value of such patent. If we are forced to grant a license to third parties with respect to any patents relevant to our business, our competitive position may be impaired, and our business, financial condition, results of operations, and growth prospects may be adversely affected.

Obtaining and maintaining our patent protection depends upon compliance with various procedural, document submission, fee payment and other requirements imposed by governmental patent agencies, and our patent protection could be reduced or eliminated for non-compliance with these requirements.

The USPTO and various foreign governmental patent agencies require compliance with a number of procedural, documentary, fee payment and other provisions during the patent prosecution process and following the issuance of a patent. In some cases, an inadvertent failure to comply with such requirements can be cured by payment of a late fee or by other means in accordance with the applicable rules. There are situations, however, in which non-compliance could result in abandonment or lapse of a patent or patent application, resulting in partial or complete loss of patent rights in the relevant jurisdiction. In such an event, competitors might be able to enter the market earlier than would otherwise have been the case if our patent were in force, which would have a material adverse effect on our business.

We may be subject to claims that our employees, consultants or advisors have wrongfully used or disclosed alleged trade secrets of their current or former employers or claims asserting ownership of what we regard as our own intellectual property.

As is common in the biotechnology and pharmaceutical industries, we employ individuals who were previously employed at other biotechnology or pharmaceutical companies, including our competitors or potential competitors. Although no claims against us are currently pending, we may be subject to claims that these employees, consultants or advisors or we have inadvertently or otherwise used or disclosed trade secrets or other proprietary information of their current or former employers. Litigation may be necessary to defend against these claims. If we fail in defending any such claims, in addition to paying monetary damages, we may lose valuable intellectual property rights or personnel. Even if we are successful in defending against such claims, litigation or other legal proceedings relating to intellectual property claims may cause us to incur significant expenses, and could distract our technical and management personnel from their normal responsibilities. In addition, there could be public announcements of the results of hearings, motions or other interim proceedings or developments, and, if securities analysts or investors perceive these results to be negative, it could have a substantial adverse effect on the price of our common stock. This type of litigation or proceeding could substantially increase our operating losses and reduce our resources available for development activities. We may not have sufficient financial or other resources to adequately conduct such litigation or proceedings. Some of our competitors may be able to sustain the costs of such litigation or proceedings more effectively than we can because of their substantially greater financial resources. Uncertainties resulting from the initiation and continuation of patent litigation or other intellectual property related proceedings could adversely affect our ability to compete in the marketplace.

In addition, while it is our policy to require our employees and contractors who may be involved in the conception or development of intellectual property to execute agreements assigning such intellectual property to us, we may be unsuccessful in executing such an agreement with each party who, in fact, conceives or develops intellectual property that we regard as our own. The assignment of intellectual property rights may not be self-executing, or the assignment agreements may be breached, and we may be forced to bring claims against third parties, or defend claims that they may bring against us, to determine the ownership of what we regard as our intellectual property. Such claims could have a material adverse effect on our business, financial condition, results of operations, and growth prospects.

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

In addition to the protection afforded by patents, we rely on trade secret protection and confidentiality agreements to protect proprietary know-how that is not patentable or that we elect not to patent, processes for which patents are difficult to enforce and any other elements of our platform technology and discovery and development processes that involve proprietary know-how, information or technology that is not covered by patents. However, trade secrets can be difficult to protect and we have limited control over the protection of trade secrets used by our collaborators and suppliers. Although we seek to protect our proprietary technology and processes, in part, by entering into confidentiality agreements with parties who have access them, such as our employees, consultants, and outside scientific advisors, contractors and collaborators, we cannot guarantee that we have entered into such agreements with each party that may have or have had access to our trade secrets or proprietary technology and processes. Despite our efforts, any of these parties might breach the agreements and intentionally or inadvertently disclose our trade secret information and we may not be able to obtain adequate remedies for such breaches. In addition, competitors may otherwise gain access to our trade secrets or independently develop substantially equivalent information and techniques. Moreover, our competitors or other third parties may independently develop equivalent knowledge, methods and know-how.

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 inside and outside the United States sometimes are less willing or unwilling to protect trade secrets. If we choose to go to court to stop a third party from using any of our trade secrets, we may incur substantial costs. These lawsuits may consume our time and other resources even if we are successful. If any of our trade secrets were determined to be lawfully obtained or independently developed by a competitor or other third party, we may not be able to prevent them from using that technology or information to compete with us. If any of our trade secrets were to be disclosed to or independently developed by a competitor or other

third party, our competitive position, business, results of operations and prospects would be materially and adversely harmed.

Intellectual property rights do not necessarily address all potential threats.

The degree of future protection for our proprietary rights is uncertain because legal means afford only limited protection and may not adequately protect our rights or permit us to gain or keep our competitive advantage. For example:

- others may be able to make or use compounds that are similar to the pharmaceutical compounds used in our product candidates but that are not covered by the claims of our patents;
- the APIs in our current product candidates will eventually become commercially available in generic drug products, and no patent protection may be available with regard to formulation or method of use;
- we, or our future licensors or collaborators, might not have been the first to file patent applications for these inventions;
- we, or our future licensors or collaborators, might not have been the first to make the inventions covered by our issued patents or pending patent applications;
- others may independently develop similar or alternative technologies or duplicate any of our technologies;
- it is possible that our current or future pending or licensed patent applications will not result in issued patents;
- it is possible that public disclosures or publications, including disclosures or publications made by us, could be used in an attempt to invalidate our patents;
- issued patents that we hold rights to may be held invalid or unenforceable, including as a result of legal challenges by our competitors or other third parties;
- our competitors or other third parties might conduct research and development activities in countries where we do not have patent rights and then use the information learned from such activities to develop competitive products for sale in our major commercial markets;
- it is possible that others may circumvent our patents;
- it is possible that there are unpublished applications or patent applications maintained in secrecy that may later issue with claims covering our products or technology similar to ours;
- the laws of foreign countries may not protect our proprietary rights to the same extent as the laws of the United States;
- the claims of our issued patents or patent applications, if and when issued, may not cover our product candidates;
- our issued patents may not provide us with any competitive advantages, may be narrowed in scope, or be held invalid or unenforceable as a result of legal challenges by third parties;
- the inventors of our patents or patent applications may become involved with competitors, develop products or processes which design around our patents, or become hostile to us or the patents or patent applications on which they are named as inventors;

- we have engaged in scientific collaborations in the past and will continue to do so in the future. Such collaborators may develop adjacent or competing products to ours that are outside the scope of our patents;

- we may not develop additional proprietary technologies for which we can obtain patent protection;

- we may choose not to pursue patent protection in order to maintain certain trade secrets or know-how, and a third party may subsequently obtain a patent covering such intellectual property;

- it is possible that product candidates or diagnostic tests we develop may be covered by third parties' patents or other exclusive rights; or

- the patents of others may have an adverse effect on our business.

Should any of these events occur, they could have a material adverse effect on our business, financial condition, results of operations and growth prospects.

Risks related to regulatory and marketing approval and other legal compliance matters

We have never obtained marketing approval for a product candidate and we may be unable to obtain, or may be delayed in obtaining, marketing approval for any of our product candidates.

We have never obtained marketing approval for a product candidate. The time required to obtain approval by the FDA and comparable foreign regulatory authorities is unpredictable but typically takes many years following the commencement of preclinical studies and clinical trials and depends upon numerous factors, including the substantial discretion of the regulatory authorities. It is possible that the FDA and comparable foreign regulatory authorities may refuse to accept for filing and substantive review any new drug applications, or NDAs, marketing authorization applications, or MAA, that we submit for our product candidates or may conclude after review of our data that our application is insufficient to obtain marketing approval of our product candidates. If the FDA, or comparable foreign regulatory authorities do not accept or approve our NDAs or MAAs for our product candidates, it may require that we conduct additional clinical, nonclinical or manufacturing validation studies and submit that data before it will reconsider our applications. Depending on the extent of these or any other regulatory authority-required studies, approval of any NDA, MAA or other application that we submit may be delayed by several years, or may require us to expend more resources than we have available. It is also possible that additional studies, if performed and completed, may not be considered sufficient by the FDA or comparable foreign regulatory authorities to approve our NDAs or our MAAs.

Any delay in obtaining, or an inability to obtain, marketing approvals would prevent us from commercializing our product candidates, generating revenues and achieving and sustaining profitability. If any of these outcomes occur, we may be forced to abandon our development efforts for our product candidates, which could significantly harm our business.

Even if we complete the necessary preclinical studies and clinical trials, the marketing approval process is expensive, time-consuming and uncertain and may prevent us, or any future collaborators, from obtaining approvals for the commercialization of some or all of our product candidates. As a result, we cannot predict when or if, and in which territories, we, or any future collaborators, will obtain marketing approval to commercialize a product candidate.

The research, testing, manufacturing, labeling, approval, selling, marketing, promotion and distribution of drugs are subject to extensive regulation by the FDA and comparable foreign regulatory authorities, whose laws and regulations may differ from country to country. We, and any future collaborators, are not permitted to market our product candidates in the United States or in other countries until we or they receive approval of an NDA from the FDA or marketing approval from comparable foreign regulatory authorities. Our product candidates are in early stages of development and are subject to the risks of failure inherent in drug development. We have not submitted an application for or received marketing approval for any of our product candidates in the United States or in any other jurisdiction. We have limited

experience in conducting and managing the clinical trials necessary to obtain marketing approvals, including FDA approval of an NDA.

The process of obtaining marketing approvals, both in the United States and abroad, is a lengthy, expensive and uncertain process. It may take many years, 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. Securing marketing approval requires the submission of extensive preclinical and clinical data and supporting information to regulatory authorities for each therapeutic indication to establish the product candidate's safety and efficacy. Securing marketing approval also requires the submission of information about the product manufacturing process to, and inspection of manufacturing facilities by, the regulatory authorities. The FDA or other comparable foreign regulatory authorities have substantial discretion and may determine that our product candidates are not safe and effective, only moderately effective or have undesirable or unintended side effects, toxicities or other characteristics that preclude our obtaining marketing approval or prevent or limit commercial use. Any marketing approval we ultimately obtain may be limited or subject to restrictions or post-approval commitments that render the approved product not commercially viable.

Our product candidates could fail to receive marketing approval, or marketing approval for our product candidates could be limited or delayed, for many reasons, including the following:

- the FDA or comparable foreign regulatory authorities may disagree with the design or implementation of our clinical trials;
- we may be unable to demonstrate to the satisfaction of the FDA or comparable foreign regulatory authorities that a product candidate is safe and effective for its proposed indication;
- the results of clinical trials may not meet the level of statistical significance required by the FDA or comparable foreign regulatory authorities for approval;
- we may be unable to demonstrate that a product candidate's clinical and other benefits outweigh its safety risks;
- the FDA or comparable foreign regulatory authorities may disagree with our interpretation of data from preclinical studies or clinical trials;
- the data collected from clinical trials of our product candidates may not be sufficient to support the submission of an NDA or other submission and applications or to obtain marketing approval in the United States or elsewhere;
- the FDA or comparable foreign regulatory authorities may fail to approve the manufacturing processes or facilities of third-party manufacturers with which we contract for clinical and commercial supplies;
- the FDA or comparable foreign regulatory authorities may fail to approve any companion diagnostics that may be required in connection with approval of our therapeutic product candidates
- the FDA or the applicable foreign regulatory agency may fail to approve the formulation, labeling and/or the specifications for our product candidate
- changes in marketing approval policies during the development period, changes in or the enactment or promulgation of additional statutes, regulations or guidance or changes in regulatory review for each submitted drug application; 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 for approval.

This lengthy approval process as well as the unpredictability of clinical trial results may result in our failing to obtain marketing approval to market APR-246, which would significantly harm our business, results of operations and

prospects. Regulatory authorities have substantial discretion in the approval process and may refuse to accept any application or may decide that our data are insufficient for approval and require additional preclinical studies, clinical trials or other studies and testing. In addition, varying interpretations of the data obtained from preclinical studies and clinical trials could delay, limit or prevent marketing approval of a product candidate. Any marketing approval we, or any collaborators we may have in the future, ultimately obtain may be limited or subject to restrictions or post-approval commitments that render the approved drug not commercially viable.

Any delay in obtaining or failure to obtain required approvals could materially adversely affect our ability or that of any collaborators we may have to generate revenue from the particular product candidate, which likely would result in significant harm to our financial position and adversely impact our stock price.

Failure to obtain marketing approval in foreign jurisdictions would prevent our product candidates from being marketed abroad. Any approval we are granted for our product candidates in the United States would not assure approval of our product candidates in foreign jurisdictions.

In order to market and sell our product candidates in the EU and many other jurisdictions, we, and any collaborators we may have in the future, must obtain separate 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 marketing approval process outside of the United States generally includes all of the risks associated with obtaining FDA approval. In addition, in many countries outside of the United States, it is required that the drug be approved for reimbursement before the drug can be approved for sale in that country. We, and any collaborators we may have in the future, may not obtain approvals from regulatory authorities outside of 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 of the United States does not ensure approval by regulatory authorities in other countries or jurisdictions or by the FDA.

The vote on June 23, 2016 by the U.K. to exit the EU, or Brexit, has created uncertainty in the global financial markets, but the eventual effects of the U.K.'s withdrawal from the EU on our business or our investment portfolios are uncertain at this time. On March 29, 2017, the Prime Minister of the U.K. notified the European Council in accordance with Article 50 of the Treaty on European Union of the U.K.'s intention to withdraw from the EU, triggering a two-year period for the negotiation of the U.K.'s withdrawal from the EU. This period was further extended subsequently. The effect of Brexit on our business and investments is uncertain as negotiations commence to determine the future items of the U.K. relationship with the EU. Furthermore, Brexit is likely to continue to adversely affect European and worldwide economic conditions and could contribute to greater instability in the global financial markets before and after the terms of the U.K.'s future relationship with the EU are settled. These effects could have an adverse effect on our business, investments and future operations in Europe. A withdrawal agreement and a political declaration were agreed at the European Council on October 17, 2019, on the terms of which the U.K. left the EU on January 31, 2020. A transition period is currently running, during which the U.K. is, with some exceptions, treated as a member of EU. After the transition period, which is expected to end on December 31, 2020, the relationship between the UK and the EU would be regulated by any agreement concluded during the transition period. A 'no-deal' Brexit scenario could therefore still occur if the U.K. and the EU do not conclude such an agreement. In a no-deal scenario, due to the U.K. leaving the single-market and in the absence of further transitional arrangements with the EU, there is a greater risk that trade between UK and EU businesses will be materially adversely affected, particularly in relation to highly regulated products such as pharmaceuticals and products of animal-origin, due to the additional regulatory burdens that are likely to be imposed on exporters/importers which may affect the availability of these products.

The consequences for the economies of the U.K. and the EU member states as a result of the U.K.'s withdrawal from the EU are unknown and unpredictable. Given the lack of comparable precedent, it is unclear what the broader macro-economic and financial implications the U.K. leaving the EU with no agreement in place on a future relationship would have.

Since a significant proportion of the regulatory framework in the U.K. is derived from EU directives and regulations, Brexit could materially impact the regulatory regime with respect to the approval of our product candidates in the U.K. 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 U.K. 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 U.K. and/or EU for our product candidates, which could significantly and materially harm our business.

We, or any future collaborators, may not be able to obtain or maintain orphan drug exclusivity for our product candidates and, even if we do, that exclusivity many not prevent the FDA or the European Commission from approving competing products.

Regulatory authorities in some jurisdictions, including the United States and the EU, may designate drugs 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 a drug 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, or a patient population greater than 200,000 in the United States where there is no reasonable expectation that the cost of developing the drug will be recovered from sales in the United States. APR-246 has received orphan drug designation from the FDA for use in the treatment of high-risk myelodysplastic syndromes, or MDS, and orphan drug designation from the European Commission for MDS, AML, and ovarian cancer. We may seek orphan drug designations for APR-246 for other indications or for other of our product candidates. There can be no assurances that we will be able to obtain such designations.

In the United States, orphan drug designation entitles a party to financial incentives such as opportunities for grant funding towards clinical trial costs, tax advantages and user-fee waivers. In addition, the company that obtains the first FDA approval for a designated orphan drug for a rare disease receives marketing exclusivity for use of that drug for the designated condition for a period of seven years. Once a product receives orphan drug exclusivity, a second product that is considered to be the same drug for the same indication generally may be approved during the exclusivity period only if the second product is shown to be “clinically superior” to the original orphan drug in that it is more effective, safer or otherwise makes a “major contribution to patient care” or the holder of exclusive approval cannot assure the availability of sufficient quantities of the orphan drug to meet the needs of patients with the disease or condition for which the drug was designated.

The European Commission can grant orphan drug product designation to products for which the sponsor can establish that it is intended for the diagnosis, prevention, or treatment of (1) a life-threatening or chronically debilitating condition affecting not more than five in 10,000 people in the European Union, or (2) a life threatening, seriously debilitating or serious and chronic condition in the European Union and that without incentives it is unlikely that sales of the drug in the European Union would generate a sufficient return to justify the necessary investment. In addition, it must be established that there is no other satisfactory method approved in the European Union of diagnosing, preventing or treating the condition, or if such a method exists, the proposed orphan drug will be of significant benefit to patients. Orphan drug designation is not a marketing authorization. It is a designation that provides a number of benefits, including fee reductions, regulatory assistance, and the possibility to apply for a centralized EU marketing authorization, as well as 10 years of market exclusivity following a marketing authorization. During this market exclusivity period, neither the EMA nor the European Commission nor the EU member states can accept an application or grant a marketing authorization for a ‘similar medicinal product.’ A ‘similar medicinal product’ is defined as a medicinal product containing a similar active substance or substances as contained in an authorized orphan medicinal product, and which is intended for the same therapeutic indication. The market exclusivity period for the authorized therapeutic indication may be reduced to six years if, at the end of the fifth year, it is established that the orphan designation criteria are no longer met, including where it is shown that the product is sufficiently profitable not to justify maintenance of market exclusivity. In addition, a competing similar medicinal product may in limited circumstances be authorized prior to the expiration of the market exclusivity period, including if it is shown to be safer, more effective or otherwise clinically superior to our product. Our product can lose orphan designation, and the related benefits, prior to us obtaining a marketing authorization if it is demonstrated that the orphan designation criteria are no longer met.

Even if we, or any future collaborators, obtain orphan drug designation for a product candidate, we, or they, may not be able to obtain or maintain orphan drug exclusivity for that product candidate. We may not be the first to obtain marketing approval of any product candidate for which we have obtained orphan drug designation for the orphan-designated indication due to the uncertainties associated with developing drug products. If this happens, marketing

approval for our product candidate may be delayed due to the first-approved product's orphan drug exclusivity, unless we demonstrate clinical superiority. We may not be able to demonstrate that our product is clinically superior to a first-approved product with orphan drug exclusivity, i.e., that it provides greater safety or efficacy or a major contribution to patient care. In addition, exclusive marketing rights in the United States may be limited if we seek approval for an indication broader than the orphan-designated indication or may be lost if the FDA later determines that the request for designation was materially defective or if we are unable to assure sufficient quantities of the product to meet the needs of patients with the rare disease or condition. Further, even if we, or any future collaborators, obtain orphan drug exclusivity for a product, that exclusivity may not effectively protect the product from competition because different drugs with different active moieties may be approved for the same condition. Even after an orphan drug is approved, the FDA can subsequently approve the same drug with the same active moiety for the same condition if the FDA concludes that the later drug is clinically superior in that it is shown to be safer, more effective or makes a major contribution to patient care or the manufacturer of the product with orphan exclusivity is unable to maintain sufficient product quantity. Orphan drug designation neither shortens the development time or regulatory review time of a drug nor gives the drug any advantage in the regulatory review or approval process.

Even if we, or any collaborators we may have in the future, obtain marketing approvals for our product candidates, the terms of approvals and ongoing regulation of our product candidates could require substantial expenditure of resources and may limit how we, or they, manufacture and market our product candidates, which could materially impair our ability to generate revenue.

Once marketing approval has been granted, an approved drug and its manufacturer and marketer are subject to ongoing review and extensive regulation. These requirements include submissions of safety and other post-marketing information and reports, user fee requirements, registration and listing requirements, requirements relating to manufacturing, quality control, quality assurance and corresponding maintenance of records and documents, requirements regarding the distribution of samples to physicians and recordkeeping. We, and any collaborators we may have in the future, must also comply with requirements concerning advertising and promotion for any of our product candidates for which we or they obtain marketing approval. Promotional communications with respect to prescription drugs are subject to a variety of legal and regulatory restrictions and must be consistent with the information in the drug's approved labeling. Thus, we, and any collaborators we may have in the future, may not be able to promote any drugs we develop for indications or uses for which they are not approved.

The FDA or comparable foreign regulatory authorities may also impose requirements for costly post-marketing studies or clinical trials and surveillance to monitor the safety or efficacy of a drug. For example, the approval may be subject to limitations on the indicated uses for which the drug may be marketed or to the conditions of approval, including the requirement to implement a REMS or comparable foreign equivalents, like the EU Risk Management Plan, or RMP, which could include requirements for a restricted distribution system. Manufacturers of approved drugs and those manufacturers' facilities are also required to comply with extensive FDA or comparable foreign regulatory authorities 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, our contract manufacturers, our future collaborators and their contract manufacturers could be subject to periodic unannounced inspections by the FDA or comparable foreign regulatory authorities to monitor and ensure compliance with cGMPs.

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

If we, and our future collaborators, are not able to comply with post-approval regulatory requirements, regulatory agencies or enforcement authorities may:

- issue warning letters;

- impose civil or criminal penalties;

- suspend regulatory approval;
- suspend any of our ongoing clinical trials;
- refuse to approve pending applications or supplements to approved applications submitted by us or our collaborators;
- impose restrictions on our operations, including closing our or our collaborators' manufacturing facilities; or
- seize or detain products or require a recall.

Any government investigation of alleged violations of law could require us to expend significant time and resources in response and could generate negative publicity. Any failure to comply with ongoing regulatory requirements may significantly and adversely affect our ability to commercialize and generate revenue from our product candidates, if approved. If regulatory sanctions are applied or if regulatory approval is withdrawn, the value of our company and our operating results will be adversely affected.

The regulatory requirements and policies may change, and additional government regulations may be enacted for which we may also be required to comply. We cannot predict the likelihood, nature or extent of government regulation that may arise from future legislation or administrative action, either in the United States or in other countries. If we or any future collaboration partner are not able to maintain regulatory compliance, we or such collaboration partner, as applicable, may face government enforcement action and our business will suffer. Moreover, our or our future collaborators' ability to market any future drugs 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.

The FDA's and other comparable regulatory authorities' policies may change and additional government regulations may be enacted that could prevent, limit or delay regulatory approval of our product candidates, which would impact our ability to generate revenue.

In December 2016, the 21st Century Cures Act, or Cures Act, was signed into law. The Cures Act, among other things, is intended to modernize the regulation of drugs and spur innovation, but its ultimate implementation is unclear. If we are slow or unable to adapt to changes in existing requirements or the adoption of new requirements or policies, or if we are not able to maintain regulatory compliance, we may lose any marketing approval that we may have obtained and we may not achieve or sustain profitability, which would adversely affect our business, prospects, financial condition and results of operations.

We also cannot predict the likelihood, nature or extent of government regulation that may arise from future legislation or administrative or executive action, either in the United States or abroad. For example, certain policies of the Trump administration may impact our business and industry. Namely, 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. Notably, 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 and approximate the total costs or savings associated with each new regulation or repealed regulation. In interim guidance issued by the Office of Information and Regulatory Affairs, within the Office of Management and Budget, on February 2, 2017, the administration indicates that the "two-for-one" provisions may apply not only to agency regulations, but also to significant agency guidance documents. In addition, on February 24, 2017, President Trump issued an Executive Order directing each affected agency to designate an agency official as a

"Regulatory Reform Officer" and establish a "Regulatory Reform Task Force" to implement the two-for-one provisions and other previously issued Executive Orders relating to the review of federal regulations; however, 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.

Any of our product candidates for which we, or our future collaborators, obtain marketing approval in the future will be subject to substantial penalties if we, or they, fail to comply with regulatory requirements or if we, or they, experience unanticipated problems with our product candidates following approval.

Any of our product candidates for which we, or our future collaborators, obtain marketing approval in the future, will be subject to continual review by the FDA or comparable foreign regulatory authorities.

For example in the United States, the FDA and other agencies, including the Department of Justice, or the DOJ, closely regulate and monitor the post-approval marketing and promotion of drugs to ensure that they are manufactured, marketed and distributed only for the approved indications and in accordance with the provisions of the approved labeling. The FDA imposes stringent restrictions on manufacturers' communications regarding off-label use and if we, or our future collaborators, do not market any of our product candidates for which we, or they, receive marketing approval for only their approved indications, we, or they, may be subject to warnings or enforcement action for off-label marketing. Violation of the FDCA and other statutes, including the False Claims Act, relating to the promotion and advertising of prescription drugs may lead to investigations or allegations of violations of federal and state healthcare fraud and abuse laws and state consumer protection laws.

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

- litigation involving patients taking our drug;
- restrictions on such drugs, manufacturers or manufacturing processes;
- restrictions on the labeling or marketing of a drug;
- restrictions on drug distribution or use;
- requirements to conduct post-marketing studies or clinical trials;
- warning letters or untitled letters;
- withdrawal of the drugs from the market;
- refusal to approve pending applications or supplements to approved applications that we submit;
- recall of drugs;
- fines, restitution or disgorgement of profits or revenues;
- suspension or withdrawal of marketing approvals;
- damage to relationships with any potential collaborators;
- restrictions on coverage by third-party payors;

- unfavorable press coverage and damage to our reputation;
- refusal to permit the import or export of drugs;
- drug seizure; or
- injunctions or the imposition of civil or criminal penalties.

Recently enacted and future legislation, and a change in existing government regulations and policies, may increase the difficulty and cost for us and our future 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 some foreign jurisdictions, there have been and continue to be 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, or the ability of our future collaborators, to effectively sell any drugs for which we, or they, 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 additional downward pressure on the price that we, or our future collaborators, may receive for any approved drugs.

In the United States, the Congress and recent presidential administrations have enacted or are considering a number of legislative and regulatory proposals to change the healthcare system in ways that could affect our ability to sell our products, if approved, and to do so effectively. Among policy makers and payors in the United States and elsewhere, there is significant interest in promoting changes in healthcare systems with the stated goals of containing healthcare costs, improving quality and expanding access.

In the United States, the pharmaceutical industry has been a particular focus of efforts to reform the healthcare system and has been significantly affected by major legislative initiatives, including the PPACA which contains provisions that may potentially affect the profitability of our products, including, for example, increased rebates for products sold to Medicaid programs, extension of Medicaid rebates to Medicaid managed care plans, mandatory discounts for certain Medicare Part D beneficiaries and annual fees based on pharmaceutical companies' share of sales to federal health care programs, and expansion of the entities eligible for discounts under the Public Health Services pharmaceutical pricing program. There have been judicial and Congressional challenges to the PPACA, as well as efforts by the Trump Administration to repeal or replace certain aspects of the PPACA that contribute to regulatory uncertainty that could affect the profitability of our products. While Congress has not enacted legislation to comprehensively repeal the PPACA, at least two bills affecting the implementation of certain provisions of the PPACA have been signed into law, including the repeal, effective January 1, 2019, of the tax-based shared responsibility payment imposed by the PPACA on certain individuals who fail to maintain qualifying health coverage for all or part of a year, which is commonly referred to as the "individual mandate." In December 2018, a federal district court in Texas ruled the individual mandate, without the penalty that was repealed effective January 1, 2019, was unconstitutional and could not be severed from the PPACA. As a result, the court ruled the remaining provisions of the PPACA were also invalid. The Fifth Circuit Court of Appeals affirmed the district court's ruling that the individual mandate was unconstitutional, but it remanded the case back to the district court for further analysis of whether the mandate could be severed from the PPACA (i.e. whether the entire PPACA was therefore also unconstitutional). The Supreme Court of the United States granted certiorari on March 2, 2020, and the case is expected to be decided in 2021.

Since January 2017, President Trump has signed several Executive Orders and other directives designed to delay the implementation of certain provisions of the PPACA or otherwise circumvent some of the requirements mandated by the PPACA. For example, on January 22, 2018, President Trump signed a continuing resolution on appropriations for fiscal year 2018 that delayed the implementation of certain fees mandated by the PPACA, including the so-called "Cadillac" tax on certain high-cost employer-sponsored health insurance plans and the annual fee imposed on certain health insurance providers.

Effective January 1, 2019, the Bipartisan Budget Act of 2018, among other things, further amended portions of the Social Security Act implemented as part of the PPACA to increase from 50% to 70% the point-of-sale discount that pharmaceutical manufacturers participating in the Coverage Gap Discount Program must provide to eligible Medicare Part D beneficiaries during the coverage gap phase of the Part D benefit, commonly referred to as the "donut hole," and to reduce standard beneficiary cost sharing in the coverage gap from 30% to 25% in most Medicare Part D plans. In the future, there may be additional challenges and/or amendments to the PPACA. It remains to be seen precisely what any new legislation will provide, when or if it will be enacted, and what impact it will have on the availability and cost of healthcare items and services, including drug products.

Other legislative changes have been proposed and adopted since PPACA was enacted. These changes include the Budget Control Act of 2011, which, among other things, led to aggregate reductions in Medicare payments to providers of up to 2% per fiscal year that started in April 2013 and, due to subsequent statutory amendments, will continue through 2027 unless additional Congressional action is taken. The American Taxpayer Relief Act of 2012, which, among other changes, reduced Medicare payments to several types of providers and increased the statute of limitations period for the government to recover overpayments to providers from three to five years. These legislative changes 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.

More recently, the cost of prescription pharmaceuticals has been the subject of considerable discussion in the United States. Congress has begun developing legislation and the Trump Administration has proposed and begun implementing regulatory reforms to further increase transparency around prices and price increases, lower out-of-pocket costs for consumers, and decrease spending on prescription drugs by government programs. Congress has conducted or is in the process of conducting inquiries into the prescription drug industry's pricing practices. While several proposed reform measures will require Congress to pass legislation to become effective, Congress and the Trump Administration have each indicated that it will continue to seek new legislative and/or regulatory measures to address prescription drug costs. At the state level, legislatures are increasingly passing legislation and states are implementing regulations designed to control spending on, and patient out-of-pocket costs for, drug products. Implementation of cost containment measures or other healthcare reforms that affect the pricing and/or availability of drug products may impact our ability to generate revenue, attain or maintain profitability, or commercialize products for which we may receive regulatory approval in the future.

We expect that these and other healthcare reform measures that may be adopted in the future may result in more rigorous coverage criteria and/or new payment methodologies, and place additional downward pressure on the price that we receive for any approved product and/or the level of reimbursement physicians receive for administering any approved product we might bring to market. Reductions in reimbursement levels and imposition of more rigorous coverage criteria or new payment methodologies may negatively impact the prices we receive or the frequency with which our products are prescribed or administered. Any coverage or reimbursement policies instituted by Medicare or other federal health care programs may result in a similar policies from private payors. The implementation of cost containment measures or other healthcare reforms may affect our ability to generate revenue, attain or maintain profitability, or commercialize our product candidates. 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.

The pricing of prescription pharmaceuticals is also subject to governmental control outside the United States. 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 may be required to conduct a clinical trial that compares the cost-effectiveness of our product candidates to that of 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 ability to generate revenues and become profitable could be impaired.

Legislative and regulatory proposals have also been made to expand post-approval requirements and restrict sales and promotional activities for drug products. We cannot be sure whether additional legislative changes will be enacted, or whether the FDA regulations, guidance or interpretations will be changed, or what the impact of such changes on the

marketing approvals of our product candidates, if any, may be. In addition, increased scrutiny by the United States Congress of the FDA's approval process may significantly delay or prevent marketing approval, as well as subject us and any future collaborators to more stringent drug labeling and post-marketing testing and other requirements.

Regulatory proposals have been made to allow the importation of prescription drugs into the United States that are approved for marketing in Canada, and potentially other countries. If such proposals become effective, and if APR-246 or another similar or equivalent drug product is approved in another ex-US jurisdiction, these regulatory proposals may impact the competition our product may face, if approved. We cannot be sure whether additional legislative changes will be enacted, or whether the FDA regulations, guidance or interpretations will be changed, or what the impact of such changes on the marketing approvals of our product candidates, if any, may be.

We may seek a breakthrough therapy designation for APR-246 or one or more of our other product candidates, but we might not receive such designation, and even if we do, such designation may not lead to a faster development or regulatory review or approval process.

We may seek a breakthrough therapy designation for APR-246 or one or more of our other product candidates. A breakthrough therapy is defined as a drug that is intended, alone or in combination with one or more other drugs, to treat a serious or life-threatening condition, and preliminary clinical evidence indicates that the drug may demonstrate substantial improvement over existing therapies on one or more clinically significant endpoints, such as substantial treatment effects observed early in clinical development. For drugs and biologics that have been designated as breakthrough therapies, interaction and communication between the FDA and the sponsor of the trial can help to identify the most efficient path for clinical development while minimizing the number of patients placed in ineffective control regimens. Drugs designated as breakthrough therapies by the FDA may also be eligible for priority review if supported by clinical data at the time the NDA is submitted to the FDA, and parts of the NDA may be submitted and reviewed on a rolling basis.

Designation as a breakthrough therapy is within the discretion of the FDA. Accordingly, even if we believe that one of our product candidates meets the criteria for designation as a breakthrough therapy, the FDA may disagree and instead determine not to make such designation. Even if we receive breakthrough therapy designation, the receipt of such designation for a product candidate may not result in a faster development or regulatory review or approval process compared to drugs considered for approval under conventional FDA procedures and does not assure ultimate approval by the FDA. In addition, even if one or more of our product candidates qualify as breakthrough therapies, the FDA may later decide that the product candidates no longer meet the conditions for qualification or decide that the time period for FDA review or approval will not be shortened.

Although we have received breakthrough therapy designation for APR-246 for the treatment of patients with myelodysplastic syndrome having a susceptible *TP53* mutation, this does not ensure that we will receive marketing approval of that marketing approval will be granted within any particular timeframe.

A fast track designation by the FDA for APR-246 may not actually lead to a faster development or regulatory review or approval process.

If a drug is intended, whether alone or in combination with one or more other drugs, for the treatment of a serious or life-threatening condition and nonclinical or clinical data demonstrate the potential to address unmet medical need for this condition, a drug sponsor may apply for FDA fast track designation. Although we have received a fast track designation for APR-246 for the treatment of patients with myelodysplastic syndrome having a *TP53* mutation, this does not ensure that we will receive marketing approval or that approval will be granted within any particular timeframe. We may not experience a faster development or regulatory review or approval process with fast track designation compared to conventional FDA procedures. In addition, the FDA may withdraw fast track designation if it believes that the designation is no longer supported by data from our clinical development program. Fast track designation alone does not guarantee qualification for the FDA's priority review procedures.

We may seek priority review designation for APR-246 or one or more of our other product candidates, but we might not receive such designation, and even if we do, such designation may not lead to a faster development or regulatory review or approval process.

If the FDA determines that a product candidate offers a treatment for a serious condition and, if approved, the product would provide a significant improvement in safety or effectiveness, the FDA may designate the product candidate for priority review. A priority review designation means that the goal for the FDA to review an application is six months from the 60-day filing date, rather than the standard review period of ten months. We may request priority review for our product candidates. The FDA has broad discretion with respect to whether or not to grant priority review status to a product candidate, so even if we believe a particular product candidate is eligible for such designation or status, the FDA may decide not to grant it. Moreover, a priority review designation does not necessarily mean a faster development or regulatory review or approval process or necessarily confer any advantage with respect to approval compared to conventional FDA procedures. Receiving priority review from the FDA does not guarantee approval within the six-month review cycle or at all.

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 could expose us to penalties, including criminal sanctions, civil penalties, contractual damages, reputational harm and diminished profits and future earnings.

Although we do not currently have any products on the market, we are subject to a variety of regulatory requirements, including healthcare statutory and regulatory requirements and enforcement by the U.S. federal and state governments and the foreign governments of the countries in which we conduct our business. Even though we are not in a position to make patient referrals and do not bill Medicare, Medicaid, or other government or commercial third-party payors, our relationships with healthcare providers, physicians and third-party payors will subject us to healthcare statutory and regulatory requirements and enforcement by the federal government and the states and foreign governments in which we conduct our business. Our future arrangements with healthcare providers, physicians and third-party payors and patients 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 our products for which we obtain marketing approval. Restrictions under applicable federal and state healthcare laws and regulations include, without limitation, the following:

- *The Federal Anti-Kickback Statute*—An intent-based federal criminal statute that prohibits, among other things, any person from knowingly and willfully soliciting, offering, receiving or paying 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, in whole or in part, by a federal health care program, such as Medicare and Medicaid. The term “remuneration” has been broadly interpreted to include anything of value. The PPACA, among other things, amended the intent requirement of the federal Anti-Kickback Statute, to clarify that a person or entity need not have actual knowledge of this statute or specific intent to violate it. The Anti-Kickback Statute applies to arrangements between pharmaceutical manufacturers on the one hand and individuals, such as prescribers, patients, purchasers, and formulary managers on the other hand, including, for example, consulting/speaking arrangements, discount and rebate offers, grants, charitable contributions, and patient support offerings, among others. A conviction for violation of the Anti-Kickback Statute can result in criminal fines and/or imprisonment and requires mandatory exclusion from participation in federal health care programs. Exclusion may be imposed if the government determines that an entity has committed acts that are prohibited by the Anti-Kickback Statute. Although there are a number of statutory exceptions and regulatory safe harbors to the federal Anti-Kickback Statute that protect certain common industry practices from prosecution, the exceptions and safe harbors are narrowly drawn, and arrangements may be subject to scrutiny or penalty if they do not fully satisfy all elements of an available exception or safe harbor. The Anti-Kickback Statute safe harbors are the subject of possible regulatory reforms. Any changes to the safe harbors may impact our future contractual and other arrangements with pharmacy benefit managers, group purchasing organizations, third-party payors, wholesalers and distributors, healthcare providers and prescribers, and other entities, as well as our future pricing strategies.

- *The Federal Civil False Claims Act*—Imposes 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 to a federal healthcare program or knowingly making using or causing to be made or used 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 $11,181 to $22,363 per false claim or statement for penalties assessed after January 29, 2018, with respect to violations occurring after November 2, 2015. Pharmaceutical companies have been investigated and/or subject to government enforcement actions asserting liability under the federal civil False Claims Act in connection with their alleged off-label promotion of drugs, purportedly concealing price concessions in the pricing information submitted to the government for government price reporting purposes (e.g., under the Medicaid Drug Rebate Program), and allegedly providing free product to customers with the expectation that the customers would bill federal health care programs for the product. In addition, the government may assert that a claim including items or services resulting from a violation of the federal Anti-Kickback Statute constitutes a false or fraudulent claim for purposes of the federal False Claims Act. As a result of a modification made by the Fraud Enforcement and Recovery Act of 2009, a claim includes “any request or demand” for money or property presented to the U.S. government. In addition, manufacturers can be held liable under the federal False Claims Act even when they do not submit claims directly to government payors if they are deemed to “cause” the submission of false or fraudulent claims. There is also the Federal Criminal False Claims Act, which is similar to the Federal Civil False Claims Act and imposes criminal liability on those that make or present a false, fictitious or fraudulent claim to the federal government.

- *The Federal Criminal Statute on False Statements Relating to Health Care Matters*—Makes it a crime to knowingly and willfully falsify, conceal, or cover up a material fact, make any materially false, fictitious, or fraudulent statements or representations, or make or use any materially false writing or document knowing the same to contain any materially false, fictitious, or fraudulent statement or entry in connection with the delivery of or payment for healthcare benefits, items, or services.

- *HIPAA Criminal Federal Health Care Fraud Statute*—Enacted as part of HIPPA, makes it a crime to knowingly and willfully execute, or attempt to execute, a scheme or artifice to defend any health care benefit program or to obtain, by means of false or fraudulent pretenses, representations, or promises, any of the money or property owned by, or under the custody or control of, any health care benefit program in connection with the delivery of or payment for healthcare benefits, items, or services.

- *The Federal Civil Monetary Penalties Law*—Authorizes the imposition of substantial civil monetary penalties against an entity, such as a pharmaceutical manufacturer, that engages in activities including, among others (1) knowingly presenting, or causing to be presented, a claim for services not provided as claimed or that is otherwise false or fraudulent in any way; (2) arranging for or contracting with an individual or entity that is excluded from participation in federal healthcare programs to provide items or services reimbursable by a federal healthcare program; (3) violations of the federal Anti-Kickback Statute; or (4) failing to report and return a known overpayment.

- *HIPAA Health Information Privacy and Security*—The Health Insurance Portability and Accountability Act of 1996, as amended by the Health Information Technology for Economic and Clinical Health Act of 2009, or HITECH, and its implementing regulations, or collectively, HIPAA, imposes privacy, security, and breach reporting obligations on certain covered entity healthcare providers, health plans, and healthcare clearinghouse as well as their business associates that perform certain services involving the use or disclosure of individually identifiable protected health information, including, among other requirements, to implement certain policies and procedures, to support certain substantive rights of patients, mandatory contractual terms and technical safeguards to protect the privacy, security and transmission of individually identifiable health information, and require notification to affected individuals and regulatory authorities of certain breaches of security of individually identifiable health information. HITECH also created tiers of civil monetary penalties, amended HIPAA to make civil and criminal penalties directly applicable to business associates, and gave state attorneys general new authority to file civil actions for damages or injunctions in U.S. federal courts to enforce the federal HIPAA laws and seek attorneys’ fees and costs associated with pursuing federal civil actions.

- *The Federal Physician Payments Sunshine Act*—Requires "applicable manufacturers" of drugs, devices, biologics, and medical supplies for which payment is available under Medicare, Medicaid or the State Children's Health Insurance Program, among others, to track and report annually to the federal government (for disclosure to the public) certain payments and other transfers of value they make to "covered recipients." The term covered recipients includes physicians, teaching hospitals, and, for reports submitted on or after January 1, 2022, physician assistants, nurse practitioners, clinical nurse specialists, certified nurse anesthetists, and certified nurse midwives. Failure to submit required information may result in civil monetary penalties.

- *The Federal Food, Drug, and Cosmetic Act*—Prohibits, among other things, the adulteration or misbranding of drugs, biologics and medical devices.

- *Analogous State and Foreign Laws*—There are state and foreign law equivalents of the above federal laws, such as the Anti-Kickback Statute and the False Claims Act, which may apply to items or services reimbursed by any third-party payor, including commercial insurers (i.e., so-called "all-payor anti-kickback laws"). Similarly, there are state and foreign laws that govern the privacy and security of health information, biometric information or more general personally identifiable information, including state health information privacy laws, data breach notification laws, marketing privacy laws, and certain comprehensive privacy legislation such as the new California Consumer Privacy Act which govern the collection, use, disclosure, and protection of health-related and other personal information, many of which differ from each other in significant ways and, with respect to state laws, are often not pre-empted by HIPAA, or govern data that we may have that is outside the scope of HIPAA, thus requiring additional compliance efforts. These privacy and data protection laws are also evolving, requiring continual evaluation and investment in compliance programs.

- *State and Foreign Laws Regulating Pharmaceutical Manufacturer Compliance Programs, Drug Price Transparency, and Other Practices*—Some state and foreign laws require pharmaceutical companies to implement compliance programs, comply with the pharmaceutical industry's voluntary compliance guidelines and the relevant compliance guidance promulgated by the federal government, or to track and report gifts, compensation, or other remuneration to physicians and other healthcare providers. Several U.S. states and localities have enacted legislation requiring pharmaceutical companies to establish marketing compliance programs, file periodic reports, and/or make periodic public disclosures on sales, marketing, pricing, clinical trials, and other activities. Other state laws prohibit certain marketing-related activities including the provision of gifts, meals or other items to certain healthcare providers, and restrict the ability of manufacturers to offer co-pay support to patients for certain prescription drugs. In addition, several recently passed state laws require disclosures related to state agencies and/or commercial purchasers with respect to certain price increases that exceed a certain level as identified in the relevant statutes. Some of these laws and regulations contain ambiguous requirements that government officials have not yet clarified. Given the lack of clarity in the laws and their implementation, our reporting actions could be subject to the penalty provisions of the pertinent federal and state laws and regulations.

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, guidance, case law or other applicable law. 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, exclusion from participation in federal health care programs, such as Medicare and Medicaid, disgorgement, reputational harm, additional oversight and reporting obligations pursuant to a corporate integrity agreement or similar agreement to resolve allegations of non-compliance with applicable laws and regulations, and the curtailment or restructuring of our operations, any of which could adversely affect our ability to market our products, if approved, and adversely impact our financial results. Although effective compliance programs can mitigate the risk of investigation and prosecution for violations of these laws and regulations, these risks cannot be entirely eliminated. Any action against us for an alleged or suspected violation could cause us to incur significant legal expenses and could divert our management's attention from the operation of our business, even if our defense is successful. If any of the physicians or other healthcare providers or entities with whom we expect to do business is found not to be in compliance with applicable laws, it may be costly to us in terms of money, time and resources, and they may be subject to criminal, civil or administrative sanctions, including exclusions from government-funded healthcare programs.

Our employees may engage in misconduct or other improper activities, including non-compliance with regulatory standards and requirements, which could cause significant liability for us and harm our reputation.

We are exposed to the risk of employee fraud or other misconduct, including intentional failures to comply with FDA regulations or similar regulations of comparable foreign regulatory authorities, provide accurate information to the FDA or comparable foreign regulatory authorities, comply with manufacturing standards we may establish, comply with federal and state healthcare fraud and abuse laws and regulations and similar laws and regulations established and enforced by comparable foreign regulatory authorities, report financial information or data accurately or 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, 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. 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, standards 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 and results of operations, including the imposition of significant fines or other sanctions.

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. Our operations involve the use of hazardous and flammable materials, including chemicals and biological materials. Our operations also produce hazardous waste products. We generally contract with third parties for the disposal of these materials and wastes. We cannot eliminate the risk of contamination or injury from these materials. In the event of contamination or injury resulting from our use of 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.

Although 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, this insurance may not provide adequate coverage against potential liabilities. We do not maintain insurance for environmental liability or toxic tort claims that may be asserted against us in connection with our storage or disposal of hazardous and flammable materials, including chemicals and biological materials.

In addition, we may incur substantial costs in order to comply with current or future environmental, health and safety laws and regulations. These current or future laws and regulations may impair our research, development or commercialization efforts. Failure to comply with these laws and regulations also may result in substantial fines, penalties or other sanctions.

Laws and regulations governing any international operations we may have in the future may preclude us from developing, manufacturing and selling certain product candidates 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 comply with numerous laws and regulations in each jurisdiction in which we plan to operate, such as the applicable anti-bribery, anti-corruption, anti-money laundering regulations. The creation and implementation of international business practices compliance programs is costly and such programs are difficult to enforce, particularly where reliance on third parties is required.

The Foreign Corrupt Practices Act, or FCPA, prohibits any U.S. individual or business from paying, offering, authorizing payment or offering of anything of value, directly or indirectly, to any foreign official, political party or candidate for the purpose of influencing any act or decision of the foreign entity in order to assist the individual or

business in obtaining or retaining business. The FCPA also obligates companies whose securities are listed in the United States to comply with certain accounting provisions requiring the company to maintain books and records that accurately and fairly reflect all transactions of the corporation, including international subsidiaries, and to devise and maintain an adequate system of internal accounting controls for international operations. The anti-bribery provisions of the FCPA are enforced primarily by the DOJ. The Securities and Exchange Commission, or SEC, is involved with enforcement of the books and records provisions of the FCPA.

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.

Violation of the FCPA can result in significant civil and criminal penalties. Indictment alone under the FCPA can lead to suspension of the right to do business with the U.S. government until the pending claims are resolved. Conviction of a violation of the FCPA can result in long-term disqualification as a government contractor. The termination of a government contract or relationship as a result of our failure to satisfy any of our obligations under laws governing international business practices would have a negative impact on our operations and harm our reputation and ability to procure government contracts. The SEC also may suspend or bar issuers from trading securities on U.S. exchanges for violations of the FCPA's accounting provisions.

We are also subject to other laws and regulations governing our international operations, including applicable import and export control regulations, economic sanctions on countries and persons administered or enforced by the U.S. government (including, without limitation, the Office of Foreign Assets Control of the U.S. Department of the Treasury), anti-money laundering laws, customs requirements and currency exchange regulations, collectively referred to as the trade control laws. We can provide no assurance that we will be completely effective in ensuring our compliance with all applicable legal requirements, including trade control laws. If we are not in compliance with applicable trade control laws, we may be subject to criminal and civil penalties, disgorgement and other sanctions and remedial measures, and legal expenses, which could have an adverse impact on our business, results of operations, financial condition and prospects. Likewise, any investigation of any potential violations of these trade control laws by U.S. or other authorities could also have an adverse impact on our reputation, our business, results of operations, financial condition and prospects.

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 drugs 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 penalties, including suspension or debarment from government contracting.

Security breaches, loss of data and other disruptions could compromise sensitive information related to our business or prevent us from accessing critical information and expose us to liability, which could adversely affect our business and our reputation.

In the ordinary course of our business, we collect and store sensitive data, including personally identifiable information, intellectual property and proprietary business information owned or controlled by ourselves and other parties. We manage and maintain our applications and data utilizing a combination of on-site systems, managed data centers and cloud-based data centers. We utilize external security and infrastructure vendors to manage our information technology systems and data centers. These applications and data encompass a wide variety of business-critical information, including research and development information, commercial information, and business and financial information. We face a number of risks relative to protecting this critical information, including loss of access or disruptions to our IT systems, inappropriate use or disclosure of protected information, inappropriate modification, and the risk of our being

unable to adequately monitor, audit and modify our controls over our critical information. This risk extends to the third-party vendors and subcontractors we use to manage this sensitive data.

The secure processing, storage, maintenance and transmission of this critical information are vital to our operations and business strategy. Although we take measures to protect sensitive data from unauthorized access, use or disclosure, and are in the process of developing policies and procedures to protect our information technology systems and confidential and proprietary information, we do not currently have any such policies and procedures formally in place and our information technology and infrastructure may be vulnerable to attacks by hackers or viruses or breached due to employee error, malfeasance or other malicious or inadvertent disruptions. Any such breach or interruption could compromise our networks and the information stored there could be accessed by unauthorized parties, manipulated, publicly disclosed, lost or stolen. Any such access, breach or other loss of information could result in legal claims or proceedings, and liability under federal or state laws that protect the privacy of personal information, such as the Health Insurance Portability and Accountability Act of 1996, or HIPAA, the Health Information Technology for Economic and Clinical Health Act, or HITECH, and regulatory penalties. Notice of breaches must be made to affected individuals, the Secretary of the Department of Health and Human Services, and for extensive breaches, notice may need to be made to the media or State Attorneys General. Such a notice could harm our reputation and our ability to compete. Although we have implemented security measures and are in the process of implementing formal, dedicated enterprise policies and procedures to prevent unauthorized access to patient data, we do not currently have any such policies and procedures formally in place and there is no guarantee we can protect our data from breach. Unauthorized access, loss or dissemination could also damage our reputation or disrupt our operations, including our ability to conduct our analyses, process claims and appeals, conduct research and development activities, collect, process and prepare company financial information, provide information about our tests and other patient and physician education and outreach efforts through our website, and manage the administrative aspects of our business.

Penalties for violations of these laws vary. For instance, penalties for failure to comply with a requirement of HIPAA and HITECH vary significantly, and include civil monetary penalties of up to $55,910 per violation, not to exceed approximately $1.68 million per calendar year for each provision of HIPAA that is violated and, in certain circumstances, criminal penalties with fines up to $250,000 per violation and/or imprisonment. However, a single breach incident can result in multiple violations, which can lead to significant financial penalties. In addition, numerous breach incidents could lead to possible penalties in excess of $1.68 million. A person who knowingly obtains or discloses individually identifiable health information in violation of HIPAA may face a criminal penalty of up to $50,000 and up to one-year imprisonment. The criminal penalties increase if the wrongful conduct involves false pretenses or the intent to sell, transfer or use identifiable health information for commercial advantage, personal gain or malicious harm.

Further, various states, such as California and Massachusetts, have implemented similar privacy laws and regulations, such as the California Confidentiality of Medical Information Act, that impose restrictive requirements regulating the use and disclosure of health information and other personally identifiable information. These laws and regulations are not necessarily preempted by HIPAA, particularly if a state affords greater protection to individuals than HIPAA. Where state laws are more protective, we have to comply with the stricter provisions. In addition to fines and penalties imposed upon violators, some of these state laws also afford private rights of action to individuals who believe their personal information has been misused. California’s patient privacy laws, for example, provide for penalties of up to $250,000 and permit injured parties to sue for damages. The interplay of federal and state laws may be subject to varying interpretations by courts and government agencies, creating complex compliance issues for us and data we receive, use and share, potentially exposing us to additional expense, adverse publicity and liability.

Further, as regulatory focus on privacy issues continues to increase and laws and regulations concerning the protection of personal information expand and become more complex, these potential risks to our business could intensify. Moreover, privacy and cybersecurity laws and regulations are evolving, and may continue to add additional compliance costs and legal risks. For example, the California legislature passed the California Consumer Protection Act (CCPA), which came into effect January 1, 2020. The CCPA requires companies doing business in California to disclose information regarding the collection and use of a consumer’s personal data, and comply with certain qualified privacy rights requests, including rights to request deletion of or to stop the sale of their personal information. While the CCPA includes certain exemptions for data protected by HIPPA or in certain research contexts, the law covers a wide range of data we my process in other contexts. The CCPA also permits the imposition of civil penalties and expands existing state

security laws by providing a private right of action for consumers in certain circumstances where consumer data is subject to a breach. The CCPA may be further amended or interpretations of the CCPA may continue to evolve with regulatory guidance. Moreover, several states are considering similar legislation. We are still evaluating whether and how the CCPA and similar evolving legislation will impact or operations and/or limit the ways in which we can provide services or use personal data collected while providing services. The U.S. Department of Health and Human Services (HHS) Office for Civil Rights, in partnership with the Healthcare and Public Health Sector Coordinating Council (HSCC), recently issued cybersecurity guidelines for healthcare organizations that reflect consensus-based, voluntary practices to cost-effectively reduce cybersecurity risks for organizations of various sizes. Although these HHS-backed guidelines entitled *"Health Industry Cybersecurity Practices; Managing Threats and Protecting Patients,"* are voluntary, they are likely to serve as an important reference point for the healthcare industry.

Compliance with U.S. and international data protection laws and regulations could cause us to incur substantial costs or require us to change our business practices and compliance procedures in a manner adverse to our business. Moreover, complying with these various laws could require us to take on more onerous obligations in our contracts, restrict our ability to collect, use and disclose data, or in some cases, impact our ability to operate in certain jurisdictions. We do not currently have formal policies and procedures in place, and have not conducted any internal or external audits, to ensure our compliance with all applicable data protection laws and regulations. Additionally, we do not currently have policies and procedures in place for assessing our third-party vendors' compliance with applicable data protection laws and regulations. Failure by us or by our third-party vendors to comply with U.S. and international data protection laws and regulations could result in government enforcement actions (which could include civil or criminal penalties), private litigation and/or adverse publicity and could negatively affect our operating results and business. Claims that we or our third-party vendors have violated individuals' privacy rights, failed to comply with data protection laws, or breached our contractual obligations, even if we or our third-party vendor, as applicable, are not found liable, could be expensive and time consuming to defend and could result in adverse publicity that could harm our business.

Any clinical trial programs we conduct or research collaborations we enter into in the European Economic Area ("EEA")/UK may subject us to European data protection laws including, the EU General Data Protection Regulation 2016/679 ("GDPR").

We are subject to the GDPR (as implemented by countries in Europe), which applies extra-territorially and implements stringent operational requirements on controllers (e.g., sponsors) and processors (e.g., CROs, laboratories) of personal data, including, for example, high standards for obtaining valid consent from individuals to process their personal data (where consent is the legal ground relied upon), the requirements to provide detailed disclosures to individuals, restrictions on transfers of personal data from the EEA/UK, short timelines for personal data breach notifications to data protection authorities, limitations on retention of personal data, additional considerations where processing health data and other "special categories of personal data" and specific obligations where third-party processors are engaged. Further, the GDPR provides that EU Member States (and the UK) may establish their own laws and regulations further restricting the processing of genetic data, biometric data, health data and other personal data, which could limit our ability to use and share such personal data or could cause our costs to increase. The GDPR imposes onerous accountability obligations requiring controllers and processors to maintain a record of their data processing activities and policies and procedures to demonstrate compliance with the GDPR. We do not currently have any formal data privacy policies and procedures in place and have not completed an assessment of whether we are in compliance with the GDPR. The GDPR also grants certain privacy rights to individuals (e.g., the right to access or erase their personal data). If our or our vendors' or service providers' privacy or data security measures fail to comply with the GDPR requirements, we may be subject to litigation, regulatory investigations, enforcement notices requiring us to stop or change the way we use personal data and/or fines of up to 20 million Euros or up to 4% of the total worldwide annual turnover of the preceding financial year, whichever is higher, as well as compensation claims for financial or non-financial loss by affected individuals, negative publicity, reputational harm and a potential loss of business and goodwill. It is possible that these laws may be interpreted and applied in a manner that is inconsistent with our practices.

Risks related to employee matters and managing growth

Our future success depends on our ability to retain our President and Chief Executive Officer, our Senior Vice President and Chief Financial Officer, our Senior Vice President and Chief Scientific Officer, Chief Medical Officer, Vice President of Business Development and other key executives and to attract, retain and motivate qualified personnel.

We are highly dependent on Christian S. Schade, our President and Chief Executive Officer, Scott M. Coiante, our Senior Vice President and Chief Financial Officer, Lars Abrahmsen, Ph.D., our Senior Vice President and Chief Scientific Officer, Eyal C. Attar, M.D., our Senior Vice President and Chief Medical Officer, and Gregory A. Korbel, Ph.D., our Vice President of Business Development, as well as the other principal members of scientific team. Our agreements with Mr. Schade, Mr. Coiante, Dr. Abrahmsen, Dr. Attar and Dr. Korbel do not prevent them from terminating their employment with us at any time. We do not maintain “key person” insurance for any of our executives or other employees. However, the loss of the services of any of these persons could impede the achievement of our research, development and commercialization objectives.

Recruiting and retaining qualified scientific, clinical, manufacturing and sales and marketing personnel will also be critical to our success. We may not be able to attract and retain these personnel on acceptable terms given the competition among numerous pharmaceutical and biotechnology companies for similar personnel. We also experience competition for the hiring of scientific and clinical personnel from universities and research institutions. In addition, we rely on consultants and advisors, including scientific and clinical advisors, to assist us in formulating our research and development and commercialization strategy. Our consultants and advisors may be employed by employers other than us and may have commitments under consulting or advisory contracts with other entities that may limit their availability to us.

Our employees may engage in misconduct or other improper activities, including non-compliance with regulatory standards and requirements, which could cause significant liability for us and harm our reputation.

We are exposed to the risk of employee fraud or other misconduct, including intentional failures to comply with FDA regulations or similar regulations of comparable foreign regulatory authorities, provide accurate information to the FDA or comparable foreign regulatory authorities, comply with manufacturing standards we may establish, comply with federal and state healthcare fraud and abuse laws and regulations and similar laws and regulations established and enforced by comparable foreign regulatory authorities, report financial information or data accurately or 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, 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. 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, standards 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 and results of operations, including the imposition of significant fines or other sanctions.

We expect to expand our development and regulatory capabilities and potentially our sales and marketing capabilities, and as a result, we may encounter difficulties in managing our growth, which could disrupt our operations.

We expect to experience significant growth in the number of our employees and the scope of our operations, particularly in the areas of drug development, clinical operations, regulatory affairs and, potentially, sales and marketing. To manage our anticipated future growth, we must continue to implement and improve our managerial, operational and financial systems, expand our facilities and continue to recruit and train additional qualified personnel. Due to our limited financial resources and the limited experience of our management team in managing a company with such anticipated

growth, we may not be able to effectively manage the expansion of our operations or recruit and train additional qualified personnel. The physical expansion of our operations may lead to significant costs and may divert our management and business development resources. Any inability to manage growth could delay the execution of our business plans or disrupt our operations.

Risks related to tax matters

We have significant deferred tax assets, which may become devalued if we do not generate sufficient future taxable income, applicable corporate tax rates are reduced or if we experience an ownership change.

Our total gross deferred tax assets as of December 31, 2019 were $19.7 million. Of that amount, $17.4 million relates to gross deferred tax assets in Aprea AB. Our anticipated activities are also expected to result in future significant net operating losses in the United States and Sweden resulting in additional deferred tax assets. Utilization of most deferred tax assets is dependent on generating sufficient future taxable income in the appropriate jurisdiction and/or entity. The company has provided a valuation allowance of $19.7 million on our net deferred tax assets as of December 31, 2019, based on all available evidence, it is considered more likely than not that all the recorded deferred tax assets will not be realized in a future period. Additionally, most of our deferred tax assets are determined by reference to applicable corporate income tax rates in Sweden or the United States. Accordingly, in the event of a reduction of any such corporate income tax rates, the carrying value of certain of our deferred tax assets would decrease.

Moreover, our ability to use our net operating losses and other deferred tax assets to offset future taxable income in Sweden and the United States may be significantly limited if we experience an ownership change. For Swedish income tax purposes, an ownership change will generally occur when one, or several shareholders together, acquire shares representing more than 50 percent of the voting power over a five year period (under special provisions in Chapter 40 of the Swedish Income Tax Act; 1999:1229). Such an ownership change results in the forfeiture of tax losses carried forward exceeding 200 percent of the cost of the change of control. In this calculation, capital contributions to the company prior to the ownership change and in the preceding two years should reduce the cost of the change of control. Due to potential ownership changes under the Swedish Income Tax Act, we may be limited in our ability to realize a tax benefit on our deferred tax assets, whether or not we attain profitability in future years.

For U.S. federal income tax purposes, an ownership change will generally occur when the percentage of our stock (by value) owned by one or more “5 percent shareholders” (as defined in the U.S. Internal Revenue Code of 1986, as amended) has increased by more than 50% over the lowest percentage owned by such shareholders at any time during the prior three years (calculated on a rolling basis). We anticipate that we will incur losses in the United States in the foreseeable future related to our research and development activities. Due to potential ownership changes under Section 382 of the Code, we may be limited in our ability to realize a tax benefit from the use of our deferred tax assets, whether or not we attain profitability in future years.

In addition, our ability to utilize any future net operating losses may be limited by the recently enacted Pub. L. 115-97, commonly known as the Tax Cuts and Jobs Act of 2017 (“TCJA”). Under the TCJA, the amount of our net operating losses that we are permitted to deduct in any taxable year is limited to 80% of our taxable income in such year, where taxable income is determined without regard to the net operating loss deduction itself, while allowing unused net operating losses to be carried forward indefinitely.

For these reasons, a material devaluation in our deferred tax assets due to insufficient taxable income, lower corporate income tax rates or ownership change would have an adverse effect on our results of operations and financial condition.

We may have taxable income as a result of the purging election we will make following the Holdco Reorganization

While not entirely clear, we intend to treat Aprea AB as having been a passive foreign investment company, or PFIC, for U.S. federal income tax purposes prior to the Holdco Reorganization and treat the Company as having succeeded to the tax basis and holding periods of those shareholders in Aprea AB that exchanged their shares for our common stock. Based on such treatment, and absent a purging election as described below, the stock of Aprea AB held by the Company would have retained its status as stock of a PFIC with respect to all periods prior to the Holdco Reorganization (the

"PFIC Taint") and therefore, absent a prior election by those shareholders to treat Aprea AB as a qualified electing fund, the Company, would have been subject to certain adverse U.S. federal income tax consequences with respect to distributions received on such stock and gain recognized on the disposition of such stock. In order to purge the PFIC Taint on the stock of Aprea AB, and avoid such adverse tax consequences, following the Holdco Reorganization we intend to make a purging election in the form of a deemed dividend election under which, for U.S. federal income tax purposes, Aprea AB will be deemed to have made a distribution to the Company of all of its current and accumulated earnings and profits as determined for U.S. federal income tax purposes. Because we do not expect Aprea AB to have had any accumulated or current year earnings and profits, we do not expect the purging election to result in any incremental U.S. federal income taxes. We note, however, that earnings and profits are determined only at the end of the taxable year and no assurance can be given that Aprea AB will not have any earnings and profits.

We may be subject to current taxation on some of the income of our foreign subsidiaries even absent any cash distributions

Because we hold directly or indirectly all of the shares of our foreign subsidiaries, including Aprea AB, such subsidiaries are treated as controlled foreign corporations ("CFC") for U.S. federal income tax purposes. For U.S. federal income tax purposes, the Company will therefore need to include in its taxable income each year Aprea AB's "subpart F income," and "global intangible low-taxed income", if any, even if no distributions are made.

Our foreign subsidiaries may directly become subject to U.S. federal income tax and be subject to a branch profits tax in the United States, which could reduce our after-tax returns and the value of our shares.

We currently intend to conduct substantially all of our businesses and operations in a manner such that our foreign subsidiaries will not be treated as engaged in a trade or business in the United States and will not be subject to additional U.S. income tax or branch profits tax. However, it is not entirely clear when a foreign subsidiary is treated as being engaged in a trade or business in the United States for U.S. federal income tax purposes. Accordingly, we cannot assure you that the Internal Revenue Service ("IRS") will not contend, perhaps successfully, that our foreign subsidiaries were engaged in a trade or business in the United States or are subject to more U.S. income tax than they currently incur. A foreign corporation deemed to be so engaged would be subject to U.S. federal income tax, as well as branch profits tax, on its income that is treated as effectively connected with the conduct of that trade or business unless the corporation is entitled to relief under an applicable tax treaty, which is determined on an annual basis.

The ongoing effects of the 2017 Tax Cuts and Jobs Act and GILTI could make our results difficult to predict.

Our effective tax rate may fluctuate in the future as a result of the TCJA, which included significant enacted changes in U.S. income tax law many aspects of which are not entirely clear and with respect to which guidance is mostly available only in proposed form. The enacted tax legislation included, among other new provisions, a reduction in the corporate tax rate, new limitations on the deductibility of net interest, the base erosion and anti-abuse minimum tax and new rules related to the global intangible low-taxed income of our foreign subsidiaries ("GILTI"). GILTI may require us to include in taxable income certain income of our foreign subsidiaries that are CFCs, though we may be eligible to claim foreign tax credits with respect to some of the taxes paid by such subsidiaries. While the U.S. tax authorities issued formal guidance as well as final and proposed regulations for GILTI, there are still certain aspects of the TCJA that remain unclear. We will continue to review the impact of GILTI and the other changes resulting from the TCJA as further guidance is issued. Any further guidance may result in changes to the interpretations and assumptions we made and actions we may take, which as a result may impact the amounts recorded with respect to international provisions of the TCJA, possibly materially.

Changes in U.S. federal income tax law and other jurisdictions could materially adversely affect an investment in our common shares.

It is possible that tax laws in the United States and other jurisdictions will be changed. It remains difficult to predict whether or when there will be any tax law changes or further guidance by the authorities in the U.S. or elsewhere in the world that will have a material adverse effect on our business.

Risks related to our common stock

Our executive officers, directors and principal stockholders will exert significant control over matters submitted to stockholders for approval. This may prevent new investors from influencing significant corporate decisions.

As of December 31, 2019, our executive officers and directors and our stockholders which own more than 5% of our outstanding common stock beneficially owned shares representing approximately 90.0% of our common stock. As a result, if these stockholders were to choose to act together, they would be able to exert significant control over matters submitted to our stockholders for approval, as well as our management and affairs. For example, these persons, if they choose to act together, would control the election of directors and approval of any merger, consolidation or sale of all or substantially all of our assets. This concentration of voting power could delay or prevent an acquisition of our company, or other significant corporate decisions, on terms that other stockholders may desire.

Provisions in our corporate charter documents and under Delaware law could make an acquisition of us, which may be beneficial to our stockholders, more difficult and may prevent attempts by our stockholders to replace or remove our current management.

Provisions in our certificate of incorporation and our bylaws may discourage, delay or prevent a merger, acquisition or other change in control of us that stockholders may consider favorable, including transactions in which common stockholders might otherwise receive a premium for our shares. These provisions could also limit the price that investors might be willing to pay in the future for shares of our common stock, thereby depressing the market price of our common stock. In addition, because our board of directors is responsible for appointing the members of our management team, these provisions may frustrate or prevent any attempts by our stockholders to replace or remove our current management by making it more difficult for stockholders to replace members of our board of directors. Among other things, these provisions:

- establish a classified board of directors such that not all members of the board are elected at one time;
- allow the authorized number of our directors to be changed only by resolution of our board of directors;
- limit the manner in which stockholders can remove directors from the board;
- establish advance notice requirements for stockholder proposals that can be acted on at stockholder meetings and nominations to our board of directors;
- require that stockholder actions must be effected at a duly called stockholder meeting and prohibit actions by our stockholders by written consent;
- limit who may call stockholder meetings;
- authorize our board of directors to issue preferred stock without stockholder approval, which could be used to institute a “poison pill” that would work to dilute the stock ownership of a potential hostile acquirer, effectively preventing acquisitions that have not been approved by our board of directors; and
- require the approval of the holders of at least 75% of the votes that all our stockholders would be entitled to cast to amend or repeal certain provisions of our charter or bylaws.

Moreover, because we are incorporated in Delaware, we are governed by the provisions of Section 203 of the Delaware General Corporation Law, which prohibits a person who owns in excess of 15% of our outstanding voting stock from merging or combining with us for a period of three years after the date of the transaction in which the person acquired in excess of 15% of our outstanding voting stock, unless the merger or combination is approved in a prescribed manner.

If securities analysts do not or do not continue to publish research or reports about our business or if they publish negative evaluations of our business, the price of our stock could decline.

The trading market for our common stock is and will rely in part on the research and reports that industry or financial analysts publish about us or our business. If one or more of the analysts who currently cover our business downgrade their evaluations of our business, or in the event we obtain additional coverage and one or more of the new analysts issues an adverse evaluation of our business, the price of our stock could decline. If one or more of these analysts cease to cover our stock, we could lose visibility in the market for our stock, which in turn could cause our stock price to decline.

The price of our common stock has been and may continue to be volatile and fluctuate substantially.

Our stock price has been and is likely to continue to be volatile. The stock market in general and the market for pharmaceutical and biotechnology companies in particular have experienced extreme volatility that has often been unrelated to the operating performance of particular companies. As a result of this volatility, our stockholders may not be able to sell our common stock at or above the price they paid for it. The market price for our common stock may be influenced by many factors, including:

- the timing and results of clinical trials of APR-246 and any of our other product candidates;
- regulatory actions with respect to our product candidates or our competitors' products and product candidates;
- the success of existing or new competitive products or technologies;
- announcements by us or our competitors of significant acquisitions, strategic partnerships, joint ventures, collaborations or capital commitments;
- establishment or termination of collaborations for our product candidates or development programs;
- failure or discontinuation of any of our development programs;
- results of clinical trials of product candidates of our competitors;
- regulatory or legal developments in the United States and other countries;
- developments or disputes concerning patent applications, issued patents or other proprietary rights;
- the recruitment or departure of key personnel;
- the level of expenses related to any of our product candidates or development programs;
- the results of our efforts to discover, develop, acquire or in-license additional product candidates or products;
- actual or anticipated changes in estimates as to financial results or development timelines;
- announcement or expectation of additional financing efforts;
- sales of our common stock by us, our insiders or other stockholders;
- variations in our financial results or those of companies that are perceived to be similar to us;
- changes in estimates or recommendations by securities analysts, if any, that cover our stock;

- changes in the structure of healthcare payment systems;
- market conditions in the pharmaceutical and biotechnology sectors;
- general economic, industry and market conditions; and
- the other factors described in this “Risk Factors” section.

We could be subject to securities class action litigation.

In the past, securities class action litigation has often been brought against a company following a decline in the market price of its securities. This risk is especially relevant for us because pharmaceutical companies have experienced significant stock price volatility in recent years. If we face such litigation, it could result in substantial costs and a diversion of management’s attention and our resources, which could harm our business.

We are an “emerging growth company” and a “smaller reporting company,” and the reduced disclosure requirements applicable to emerging growth companies or smaller reporting companies may make our common stock less attractive to investors.

We are an “emerging growth company,” as defined in the Jumpstart Our Business Startups Act of 2012, or the JOBS Act. We may remain an emerging growth company for up to five years, or until such earlier time as we have more than $1.07 billion in annual revenue, the market value of our stock held by non-affiliates is more than $700 million or we issue more than $1 billion of non-convertible debt over a three-year period. For so long as we remain an emerging growth company, we are permitted and intend to rely on exemptions from certain disclosure requirements that are applicable to other public companies that are not emerging growth companies. These exemptions include not being required to comply with the auditor attestation requirements of Section 404 of the Sarbanes-Oxley Act of 2002, or Section 404, not being required to comply with any requirement that may be adopted by the Public Company Accounting Oversight Board regarding mandatory audit firm rotation or a supplement to the auditor’s report providing additional information about the audit and the financial statements, being permitted to present only two years of audited financial statements and a correspondingly reduced “Management’s Discussion and Analysis of Financial Condition and Results of Operations” disclosure, reduced disclosure obligations regarding executive compensation and exemptions from the requirements of holding a nonbinding advisory vote on executive compensation and shareholder approval of any golden parachute payments not previously approved. We cannot predict whether investors will find our common stock less attractive if we rely on these exemptions. If some investors find our common stock less attractive as a result, there may be a less active trading market for our common stock and our stock price may be more volatile.

In addition, the JOBS Act provides that an emerging growth company can take advantage of an extended transition period for complying with new or revised accounting standards. An emerging growth company can therefore delay the adoption of certain accounting standards until those standards would otherwise apply to private companies. However, we are choosing to “opt out” of such extended transition period, and, as a result, we will comply with new or revised accounting standards on the relevant dates on which adoption of such standards is required for public companies that are not emerging growth companies. The JOBS Act provides that our decision to opt out of the extended transition period for complying with new or revised accounting standards is irrevocable.

We are also a “smaller reporting company,” as such term is defined in Rule 12b-2 of the Exchange Act, meaning that the market value of our common stock held by non-affiliates is less than $700 million and our annual revenue is less than $100 million during the most recently completed fiscal year. We may continue to be a smaller reporting company if either (i) the market value of our common stock held by non-affiliates is less than $250 million or (ii) our annual revenue is less than $100 million during the most recently completed fiscal year and the market value of our common stock held by non-affiliates is less than $700 million. If we are a smaller reporting company at the time we cease to be an emerging growth company, we may continue to rely on exemptions from certain disclosure requirements that are available to smaller reporting companies. Specifically, as a smaller reporting company we may choose to present only the two most recent fiscal years of audited financial statements in our Annual Report on Form 10-K and, similar to emerging growth companies, smaller reporting companies have reduced disclosure obligations regarding executive compensation.

We continue to incur increased costs as a result of operating as a public company as we become subject to additional laws, regulations and listing exchange standards, and our management will continue to be required to devote substantial time to new compliance initiatives.

As a public company, and particularly after we are no longer an "emerging growth company" or a "smaller reporting company," we will incur significant legal, accounting and other expenses that we did not incur as a private company. In addition, the Sarbanes-Oxley Act of 2002 and rules subsequently implemented by the SEC and NASDAQ have imposed various requirements on public companies, including establishment and maintenance of effective disclosure and financial controls and corporate governance practices. Our management and other personnel will need to devote a substantial amount of time to these compliance initiatives. Moreover, these rules and regulations will increase our legal and financial compliance costs and will make some activities more time-consuming and costly. For example, we expect that these rules and regulations may make it more difficult and more expensive for us to obtain director and officer liability insurance.

Pursuant to Section 404, we are required to furnish a report by our management on our internal control over financial reporting, including an attestation report on internal control over financial reporting issued by our independent registered public accounting firm. However, while we remain an emerging growth company, we will not be required to include an attestation report on internal control over financial reporting issued by our independent registered public accounting firm. To achieve compliance with Section 404 within the prescribed period, we will be engaged in a process to document and evaluate our internal control over financial reporting, which is both costly and challenging. In this regard, we will need to continue to dedicate internal resources, potentially engage outside consultants and adopt a detailed work plan to assess and document the adequacy of internal control over financial reporting, continue steps to improve control processes as appropriate, validate through testing that controls are functioning as documented and implement a continuous reporting and improvement process for internal control over financial reporting. 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.

Accounting principles and related pronouncements, implementation guidelines and interpretations we apply to a wide range of matters that are relevant to our business, including, but not limited to, revenue recognition, leases and stock-based compensation, are complex and involve subjective assumptions, estimates and judgments by our management. Changes in accounting pronouncements or their interpretation or changes in underlying assumptions, estimates or judgments by our management could significantly change our reported or expected financial performance.

Because we do not anticipate paying any cash dividends on our common stock for the foreseeable future, capital appreciation, if any, of our common stock may be investors' sole source of gain.

We have never declared or paid cash dividends on our common stock. We currently intend to retain all of our future earnings, if any, to finance the growth and development of our business. In addition, the terms of any future debt agreements may preclude us from paying dividends. As a result, capital appreciation, if any, of our common stock will be investors' sole source of gain for the foreseeable future.

Sales of a substantial number of shares of our common stock by our existing stockholders in the public market could cause our stock price to fall.

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 shares, could reduce the market price of our common stock. As of December 31, 2019, we have outstanding 21,022,752 shares of common stock.

Approximately 14,200,000 shares of our common stock are currently restricted as a result of securities laws or lock-up agreements but will be able to be sold after the expiration of such lock-ups or compliance with applicable exemptions from securities laws. Moreover, holders of approximately 14,200,000 shares of our common stock will have rights, subject to certain conditions, to require us to file registration statements covering their shares or to include their shares in registration statements that we may file for ourselves or other stockholders. We also intend to register all shares of

common stock that we may issue under our equity compensation plans. Once we register these shares, they can be freely sold in the public market upon issuance, subject to volume limitations applicable to affiliates and the lock-up agreements executed in connection with our IPO.

Our certificate of incorporation designates the state courts in the State of Delaware or, if no state court located within the State of Delaware has jurisdiction, the federal court for the District of Delaware, as the sole and exclusive forum for certain types of actions and proceedings that may be initiated by our stockholders, which could discourage lawsuits against the company and our directors, officers and employees.

Our certificate of incorporation provides that, unless we consent in writing to the selection of an alternative forum, the Court of Chancery of the State of Delaware (or, if the Court of Chancery does not have jurisdiction, the federal district court for the District of Delaware) will be the sole and exclusive forum for any derivative action or proceeding brought on our behalf under Delaware law, any action asserting a claim of breach of a fiduciary duty owed by any of our directors, officers or employees to our company or our stockholders, any action asserting a claim against us arising pursuant to any provision of the Delaware General Corporation Law or our certificate of incorporation or bylaws, any action asserting a claim against us governed by the internal affairs doctrine, or any other action asserting an "internal corporate claim," as defined in Section 115 of the Delaware General Corporation Law. These exclusive-forum provisions do not apply to claims under the Securities Act of 1933, as amended, or the Securities Act, or the Exchange Act. This exclusive forum provision may limit the ability of our stockholders to bring a claim in a judicial forum that such stockholders find favorable for disputes with us or our directors, officers or employees, which may discourage such lawsuits against us and our directors, officers and employees. If a court were to find the exclusive-forum provision in our certificate of incorporation to be inapplicable or unenforceable in an action, we may incur additional costs associated with resolving the dispute in other jurisdictions, which could harm our results of operations.

Item 1B. Unresolved Staff Comments

None.

Item 2. Properties

We have facilities in Boston, Massachusetts and Stockholm, Sweden. Our Boston facilities consist of office space of approximately 2,295 square feet under an operating lease agreement that expires in 2021. Our Stockholm facilities consist of office and laboratory space of approximately 3,980 square feet under an operating lease agreement that expires in 2022. We believe that are current facilities are suitable and adequate to meet our current needs. We believe that suitable additional or substitute space will be available as needed to accommodate any potential expansion of our operations.

Item 3. Legal Proceedings

None.

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 and Holders of Record

Our common stock has been listed on the Nasdaq Global Select Market under the symbol "APRE" since October 3, 2019.

As of March 27, 2020, we had 29 holders of record of our common stock. The actual number of shareholders is greater than this number of record holders and includes shareholders who are beneficial owners but whose shares are held in street name by brokers and other nominees. The number of holders of record also does not include shareholders whose shares may be held in trust by other entities.

Dividends

We have never declared or paid a cash dividend on our capital stock. We currently intend to retain any future earnings and do not expect to pay any dividends in the foreseeable future. Any future determinations to pay cash dividends will be made at the discretion of our board of directors, subject to applicable laws, and will depend on a number of factors, including our financial condition, results of operations, capital requirements, contractual restrictions, general business conditions, and any other factors that our board may deem relevant.

Securities Authorized for Issuance under Equity Compensation Plans

Information regarding the Securities Authorized for Issuance under our Equity Compensation Plans will be included in an amendment to this Annual Report in Form 10-K or incorporated by reference from our definitive proxy statement to be filed pursuant to Rule 14A.

Stock Performance Graph

As a smaller reporting company, we are not required to provide the information requested by this item pursuant to Item 201 of Regulation S-K.

Unregistered Sales of Equity Securities and Use of Proceeds

Unregistered sales of equity securities

In connection with our IPO, we engaged in a series of transactions, which we refer to collectively as the HoldCo Reorganization, whereby Aprea AB became a wholly-owned subsidiary of Aprea Therapeutics, Inc. In connection with the HoldCo Reorganization, we issued an aggregate of 736,418 shares of common stock and 8,119,855 shares of preferred stock to the equity holders of Aprea AB in exchange for their shares of Aprea AB and options to purchase an aggregate of 2,930,234 shares of our common stock in substitution for outstanding options to purchase shares of Aprea AB.

In connection with our formation and initial capitalization on July 11, 2019, we issued 100 shares of our common stock to Chris Schade, our Chief Executive Officer, for an aggregate purchase price of $100.

The issuance of the securities in connection with the HoldCo Reorganization and our initial capitalization did not involve any underwriters, underwriting discounts or commissions or a public offering, and such issuance was exempt from registration requirements pursuant to Section 4(a)(2) of the Securities Act.

From July 1, 2019 through September 30, 2019, we granted stock options to purchase an aggregate of 208,440 shares of our common stock at a weighted-average exercise price of $10.95 per share to certain employees.

We deemed the grants as exempt pursuant to Section 4(a)(2) of the Securities Act or to be exempt from registration under the Securities Act in reliance on Rule 701 of the Securities Act as offers and sales of securities under compensatory benefit plans and contracts relating to compensation in compliance with Rule 701. Each of the recipients of securities in any transaction exempt from registration either received or had adequate access, through employment, business or other relationships, to information about us.

Use of proceeds from registered securities

On October 7, 2019, after the quarter end, we completed our IPO, in which we sold 6,516,667 shares of common stock, $0.001 par value per share, which included the exercise in full by the underwriters of their option to purchase an additional 850,000 shares of common stock, at a price to the public of $15.00 per share. The offer and sale of the shares in the IPO was registered under the Securities Act pursuant to registration statements on Form S-1 (File No. 333-233662), which was filed with the SEC on September 6, 2019 and amended subsequently and declared effective on October 2, 2019, and Form S-1MEF, which was filed and declared effective with the SEC on October 2, 2019. The underwriters of the offering were J.P. Morgan Securities LLC, Morgan Stanley & Co. LLC and RBC Capital Markets, LLC.

Our registration statements relating to the IPO registered common stock with a maximum aggregate offering price of up to $103,500,005. We raised approximately $90.9 million in proceeds after deducting underwriting discounts and commissions of $6.8 million but before deducting other offering expenses. No offering expenses were paid directly or indirectly to any of our directors of officers (or their associates) or persons owning ten percent or more of any class of our equity securities or to any other affiliates.

To date, we have not used any of the net proceeds from our IPO. There has been no material change in the planned use of proceeds from our IPO, as described in our final prospectus filed with the SEC on October 4, 2019 pursuant to Rule 424(b) under the Securities Act.

Repurchases of equity securities by the issuer

None.

Item 6. Selected Financial Data

The following table sets forth our selected financial data for the periods indicated. You should read the following selected financial data in conjunction with our audited financial statements and the related notes thereto included elsewhere in this Annual Report and the "Management's Discussion and Analysis of Financial Condition and Results of Operations" section of this Annual Report.

The consolidated statement of operations data for the years ended December 31, 2019, 2018 and 2017, and the consolidated balance sheet data as of December 31, 2019, 2018 and 2017, are derived from our audited financial statements included elsewhere in this Annual Report. Our historical results are not necessarily indicative of the results that may be expected in the future

	Years ended December 31,		
	2019	2018	2017
Consolidated Statement of Operations Data:			
Operating expenses:			
Research and development	$ 20,950,672	$ 14,194,732	$ 13,392,631
General and administrative	8,593,626	2,294,671	2,459,744
Total operating expenses	29,544,298	16,489,403	15,852,375
Other income (expense):			
Interest expense	156,351	(182)	(15)
Foreign currency gain	1,328,140	961,316	662,140
Total other income (expense)	1,484,491	961,134	662,125
Net loss	$(28,059,807)	$(15,528,269)	$(15,190,250)
Net loss per share attributable to common stockholders, basic and diluted(1)	$ (4.67)	$ (13.45)	$ (13.17)
Weighted average common shares outstanding, basic and diluted(1)	6,002,486	1,154,368	1,153,069

(1) See Note 2 to our audited financial statements included elsewhere in this prospectus for an explanation of the method used to calculate basic and diluted net loss per share as well as the weighted-average number of common shares used in the computation of the per share amounts.

	December 31,		
	2019	2018	2017
Consolidated Balance Sheet Data:			
Cash and cash equivalents	$ 130,088,869	$ 65,675,931	$ 24,401,488
Working capital(1)	123,983,013	61,129,968	20,430,334
Total assets	133,607,885	66,022,638	24,761,804
Total liabilities	9,364,355	4,868,109	4,301,013
Convertible preferred stock	—	112,590,631	56,225,986
Total stockholders' equity (deficit)	124,243,530	(51,436,102)	(35,765,195)

(1) We define working capital as current assets less current liabilities.

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

The following discussion and analysis of financial condition and results of operations is provided to enhance the understanding of, and should be read in conjunction with Part I, Item I, "Business" and Item 8, 'Financial Statements and Supplementary Data." For information on risks and uncertainties related to our business that may make past performance not indicative of future results or cause actual results to differ materially from any forward looking statements, see "Special Note Regarding Forward-Looking Statements," and Part I, Item 1A, 'Risk Factors."

Overview

We are a clinical-stage biopharmaceutical company focused on developing and commercializing novel cancer therapeutics that reactivate mutant p53 tumor suppressor protein. p53 is the protein expressed from the *TP53* gene, the most commonly mutated gene in cancer. We believe that mutant p53 is an attractive therapeutic target due to the high incidence of p53 mutations across a range of cancer types and its involvement in key cellular activities such as apoptosis. Cancer patients with mutant p53 face a significantly inferior prognosis even when treated with the current standard of care, and a large unmet need for these patients remains. Our lead product candidate, APR-246, is a small molecule p53 reactivator that is in late-stage clinical development for hematologic malignancies, including myelodysplastic syndromes, or MDS, and acute myeloid leukemia, or AML. APR-246 has received Orphan Drug, Fast Track and Breakthrough designations from the FDA for MDS, and Orphan Drug designation from the European Commission for MDS, AML and ovarian cancer, and we believe APR-246 will be a first-in-class therapy if approved by applicable regulators. We have commenced a pivotal Phase 3 trial of APR-246 with azacitidine for frontline treatment of *TP53* mutant MDS and expect initial data from this trial in the second half of 2020. Our pivotal Phase 3 trial is supported by data from two ongoing Phase 1b/2 investigator initiated trials, one in the U.S. and one in France, testing APR-246 with azacitidine as frontline treatment in *TP53* mutant MDS and AML patients.

Aprea Therapeutics AB, or Aprea AB, was originally incorporated in 2002 and commenced principal operations in 2006. We incorporated Aprea Therapeutics, Inc. (the "Company") in May 2019. In September 2019 we completed a corporate reorganization and, as a result, all of the issued and outstanding stock of Aprea AB was exchanged for common stock, preferred stock or options, as applicable, of the Company. As a result of such transactions, Aprea AB became a wholly-owned subsidiary of the Company.

We have devoted substantially all of our resources to developing our product candidates, including APR-246, building our intellectual property portfolio, business planning, raising capital and providing general and administrative support for these operations. To date, we have financed our operations through private placements of preferred stock and the net proceeds received from the initial public offering (IPO) of our common stock. Through December 31, 2019, we had received net proceeds of approximately $223.8 million from our sales of preferred and common stock.

Since our inception, we have incurred significant losses on an aggregate basis. Our ability to generate product revenue sufficient to achieve profitability will depend on the successful development and eventual commercialization of one or more of our product candidates. Our net losses were $28.1 million, $15.5 million and $15.2 million for the years ended December 31, 2019, 2018 and 2017, respectively. As of December 31, 2019, we had an accumulated deficit of $90.5 million. These losses have resulted primarily from costs incurred in connection with research and development activities, patent investment, and general and administrative costs associated with our operations. We expect to continue to incur significant expenses and increasing operating losses for at least the next several years.

We anticipate that our expenses will increase substantially if and as we:

- conduct our current and future clinical trials and additional preclinical research of APR-246;
- initiate and continue research and preclinical and clinical development of our other product candidates;
- seek to identify and develop additional product candidates;

- seek marketing approvals for any of our product candidates that successfully complete clinical trials, if any;
- establish a sales, marketing, manufacturing and distribution infrastructure to commercialize any products for which we may obtain marketing approval;
- require the manufacture of larger quantities of our product candidates for clinical development and potentially commercialization;
- maintain, expand, protect and enforce our intellectual property portfolio;
- acquire or in-license other drugs and technologies;
- defend against any claims of infringement, misappropriation or other violation of third-party intellectual property;
- hire and retain additional clinical, quality control and scientific personnel;
- add operational, financial and management information systems and personnel, including personnel to support our drug development, any future commercialization efforts and our transition to a public company; and
- continue to operate as a public company.

Furthermore, if we obtain marketing approval for any of our product candidates, we expect to incur significant commercialization expenses related to product manufacturing, marketing, sales and distribution.

As a result, we will need additional financing to support our continuing operations. Until such time as we can generate significant revenue from product sales, if ever, we expect to finance our operations through a combination of public or private equity or debt financings or other sources, which may include collaborations with third parties. We may be unable to raise additional funds or enter into other agreements or arrangements when needed on favorable terms, or at all. If we fail to raise capital or enter into such agreements as and when needed, we may have to significantly delay, scale back or discontinue the development or commercialization of one or more of our product candidates.

Because of the numerous risks and uncertainties associated with product development, we are unable to predict the timing or amount of increased expenses or when or if we will be able to achieve or maintain profitability. Even if we are able to generate revenue from product sales, we may not become profitable. If we fail to become profitable or are unable to sustain profitability on a continuing basis, then we may be unable to continue our operations at planned levels and be forced to reduce or terminate our operations.

As of December 31, 2019, we had cash and cash equivalents of $130.1 million. We believe that our existing cash and cash equivalents, will enable us to fund our operating expenses and capital expenditure requirements into 2023. We have based this estimate on assumptions that may prove to be wrong, and we could exhaust our available capital resources sooner than we expect. See “—Liquidity and Capital Resources.”

Components of our results of operations

Revenue

We have not generated any revenue from product sales and do not expect to generate any revenue from the sale of products in the near future. If our development efforts for APR-246 or other product candidates that we may develop in the future are successful and result in marketing approval or collaboration or license agreements with third parties, we may generate revenue in the future from a combination of product sales or payments from collaboration or license agreements that we may enter into with third parties.

Operating expenses

Our expenses since inception have consisted solely of research and development costs and general and administrative costs.

Research and development expenses

Research and development expenses consist primarily of costs incurred for our research activities, including our discovery efforts, and the development of our product candidates, and include:

- expenses incurred under agreements with third parties, including contract research organizations, or CROs, that conduct research, preclinical activities and clinical trials on our behalf as well as contract manufacturing organizations, or CMOs, that manufacture our product candidates for use in our preclinical and clinical trials;
- salaries, benefits and other related costs, including stock-based compensation expense, for personnel engaged in research and development functions;
- costs of outside consultants, including their fees, stock-based compensation and related travel expenses;
- costs of laboratory supplies and acquiring, developing and manufacturing preclinical study and clinical trial materials;
- expenses related to compliance with regulatory requirements; and
- facility-related expenses, which include direct depreciation costs and allocated expenses for rent and maintenance of facilities and other operating costs.

We expense research and development costs as incurred. We recognize costs for certain development activities, such as clinical trials, based on an evaluation of the progress to completion of specific tasks using data such as patient enrollment, clinical site activations, or information provided to us by our vendors and our clinical investigative sites. Payments for these activities are based on the terms of the individual agreements, which may differ from the pattern of costs incurred, and are reflected in our financial statements as prepaid or accrued research and development expenses.

We typically use our employee and infrastructure resources across our development programs. We track outsourced development costs and payments made to our research partners by product candidate or development program, but we do not allocate personnel costs or other internal costs to specific development programs or product candidates.

Research and development activities are central to our business model. Product candidates in later stages of clinical development generally have higher development costs than those in earlier stages of clinical development, primarily due to the increased size and duration of later-stage clinical trials. We expect that our research and development expenses will continue to increase for the foreseeable future as we initiate additional clinical trials of APR-246, pursue later stages of clinical development of APR-246, initiate clinical trials for product candidates other than APR-246 and continue to discover and develop additional product candidates.

We cannot determine with certainty the duration and costs of the current or future clinical trials of our product candidates or if, when, or to what extent we will generate revenue from the commercialization and sale of any our product candidates for which we obtain marketing approval. We may never succeed in obtaining marketing approval for any of our product candidates. The duration, costs and timing of clinical trials and development of our product candidates will depend on a variety of factors, including:

- the scope, rate of progress, expense and results of our ongoing clinical trials of APR-246, as well as of any future clinical trials of APR-246 or other product candidates and other research and development activities that we may conduct;

- uncertainties in clinical trial design and patient enrollment rates;
- significant and changing government regulation and regulatory guidance;
- the timing and receipt of any marketing approvals; and
- the expense of filing, prosecuting, defending and enforcing any patent claims and other intellectual property rights.

A change in the outcome of any of these variables with respect to the development of a product candidate could mean a significant change in the costs and timing associated with the development of that product candidate. For example, if the U.S. Food and Drug Administration, or FDA, or another regulatory authority were to require us to conduct clinical trials beyond those that we anticipate will be required for the completion of clinical development of a product candidate, or if we experience significant trial delays due to patient enrollment or other reasons, we would be required to expend significant additional financial resources and time on the completion of clinical development.

We are currently conducting multiple clinical trials of APR-246: our Phase 3 trial in the United States for the treatment of *TP53* mutant MDS with azacitidine, our Phase 1b/2 trials in the United States and France for the treatment of MDS and AML with azacitidine, and our Phase 2 trial of post-transplant maintenance therapy with azacitidine in MDS and AML. At this time, we cannot reasonably estimate the cost for initiating and completing other clinical trials of APR-246 and preclinical studies of APR-246, as it will be highly dependent on the clinical data from ongoing clinical trials as well as any target disease subpopulations chosen for further evaluation.

General and administrative expenses

General and administrative expenses consist primarily of salaries and other related costs, including stock-based compensation, for personnel in our executive, finance, corporate and business development and administrative functions. General and administrative expenses also include legal fees relating to patent and corporate matters; professional fees for accounting, auditing, tax and consulting services; insurance costs; travel expenses; and facility-related expenses, which include direct depreciation costs and allocated expenses for rent and maintenance of facilities and other operating costs.

We expect that our general and administrative expenses will increase in the future as we increase our general and administrative personnel headcount to support personnel in research and development and to support our operations generally as we increase our research and development activities and activities related to the potential commercialization of our product candidates. We also expect to incur increased expenses associated with being a public company, including costs of accounting, audit, legal, regulatory and tax-related services associated with maintaining compliance with exchange listing and SEC requirements; director and officer insurance costs; and investor and public relations costs.

Other income and expense

Interest income and expense

Interest income consists of income earned on our cash and cash equivalents. Interest expense consists of bank charges and fees incurred on our cash and cash equivalents. Our interest income will initially increase as our investment balances will be higher due to the cash proceeds received from our IPO. Such interest income will then decrease as our cash balance decreases as we continue to fund our operations.

Foreign currency gain

Our consolidated financial statements are presented in U.S. dollars, which is our reporting currency. The financial position and results of operations of our subsidiaries Aprea AB and Aprea Personal AB are measured using the foreign subsidiaries' local currency as the functional currency. Aprea AB cash accounts holding U.S. dollars are remeasured based upon the exchange rate at the date of remeasurement with the resulting gain or loss included in the consolidated statement of operations and comprehensive loss. Expenses of such subsidiaries have been translated into U.S. dollars at

average exchange rates prevailing during the period. Assets and liabilities have been translated at the rates of exchange on the consolidated balance sheet date. The resulting translation gain and loss adjustments are recorded directly as a separate component of stockholders' equity and as other comprehensive loss on the consolidated statement of operations and comprehensive loss.

Income taxes

Since Aprea AB's inception in 2002, we have not recorded any U.S. federal, state or foreign income tax expense or benefits for the net losses we have incurred in any year, due to our uncertainty of realizing a benefit from those items. We have provided a valuation allowance for the full amount of the net deferred tax assets as, based on all available evidence, it is considered more likely than not that all the recorded deferred tax assets will not be realized in a future period. At December 31, 2019, we had $89.9 million, $7.4 million and $5.8 million of foreign, federal and state net operating loss carryforwards, respectively, that expire at various dates through 2037. Certain of these foreign, federal and state net operating loss carryforwards may be subject to Internal Revenue Code Section 382 or similar provisions, which impose limitations on their utilization amounts.

Critical accounting policies and use of estimates

Our management's discussion and analysis of financial condition and results of operations is based on our financial statements, which have been prepared in accordance with generally accepted accounting principles in the United States. The preparation of our financial statements and related disclosures requires us to make estimates and assumptions that affect the reported amounts of assets and liabilities, costs and expenses and the disclosure of contingent assets and liabilities in our financial statements. We base our estimates on historical experience, known trends and events and various other factors that we believe are reasonable under the circumstances, the results of which form the basis for making judgments about the carrying values of assets and liabilities that are not readily apparent from other sources. We evaluate our estimates and assumptions on an ongoing basis. Our actual results may differ from these estimates under different assumptions or conditions.

While our significant accounting policies are described in more detail in the notes to our financial statements, we believe that the following accounting policies are those most critical to the judgments and estimates used in the preparation of our financial statements.

Accrued research and development expenses

As part of the process of preparing our financial statements, we are required to estimate our accrued research and development expenses at each balance sheet. This process involves reviewing open contract and purchase orders, communicating with our personnel to identify services that have been performed on our behalf and estimating the level of service performed and the associated costs incurred for the services when we have not yet been invoiced or otherwise notified of the actual costs. The majority of our service providers invoice us in arrears for services performed, on a pre-determined schedule or when contractual milestones are met; however, some require advanced payments. We make estimates of our accrued expenses as of each balance sheet date in our financial statements based on facts and circumstances known to us at that time. Examples of estimated accrued research and development expenses include fees paid to:

- CROs in connection with performing research activities on our behalf and conducting preclinical studies and clinical trials on our behalf;
- investigative sites or other service providers in connection with clinical trials;
- vendors in connection with preclinical and clinical development activities; and
- vendors related to product manufacturing and development and distribution of preclinical and clinical supplies.

We base our expenses related to preclinical studies and clinical trials on our estimates of the services received and efforts expended pursuant to quotes and contracts with multiple CROs that conduct and manage preclinical studies and clinical trials on our behalf. The financial terms of these agreements are subject to negotiation, vary from contract to contract and may result in uneven payment flows. There may be instances in which payments made to our vendors will exceed the level of services provided and result in a prepayment of the expense. Payments under some of these contracts depend on factors such as the successful enrollment of patients and the completion of clinical trial milestones. In accruing fees, we estimate the time period over which services will be performed, enrollment of patients, number of sites activated and the level of effort to be expended in each period. If the actual timing of the performance of services or the level of effort varies from our estimate, we adjust the accrual or amount of prepaid expense accordingly. Although we do not expect our estimates to be materially different from amounts actually incurred, our understanding of the status and timing of services performed relative to the actual status and timing of services performed may vary and may result in us reporting amounts that are too high or too low in any particular period. To date, we have not made any material adjustments to our prior estimates of accrued research and development expenses.

Stock-based compensation

We measure stock options and other stock-based awards granted to employees and directors based on their fair value on the date of the grant and recognize compensation expense of those awards, net of estimated forfeitures, over the requisite service period, which is generally the vesting period of the respective award. We apply the straight-line method of expense recognition to all awards with only service-based vesting conditions and apply the graded-vesting method to all awards with performance-based vesting conditions or to awards with both service-based and performance-based vesting conditions.

For stock-based awards granted to non-employees, compensation expense is recognized over the period during which services are rendered by such non-employees until completed in accordance with the FASB issued ASU No. 2018-07, Compensation-Stock Compensation (Topic 718): Improvements to Nonemployee Share-Based Payment Accounting. The new standard largely aligns the accounting for share-based payment awards issued to employees and nonemployees by expanding the scope of ASC 718 to apply to nonemployee share-based transactions, as long as the transaction is not effectively a form of financing.

We estimate the fair value of each stock option grant on the date of grant using the Black-Scholes option-pricing model, which uses as inputs the fair value of our common stock and assumptions we make for the volatility of our common stock, the expected term of our stock options, the risk-free interest rate for a period that approximates the expected term of our stock options and our expected dividend yield.

Determination of fair value of common stock

As a privately held company (through October 2, 2019), there had been no public market for our common stock, the estimated fair value of our common stock had been determined by our board of directors as of the date of each option grant, with input from management, considering our most recently available third-party valuations of common stock and our board of directors' assessment of additional objective and subjective factors that it believed were relevant and which may have changed from the date of the most recent valuation through the date of the grant. These third-party valuations were performed in accordance with the guidance outlined in the American Institute of Certified Public Accountants' Accounting and Valuation Guide, *Valuation of Privately-Held-Company Equity Securities Issued as Compensation*. Our common stock valuations were prepared using a hybrid method, which used market approaches to estimate our enterprise value. The hybrid method is a probability-weighed expected return method, or PWERM, where the equity value in one or more scenarios is calculated using an option-pricing method, or OPM. The OPM treats common stock and preferred stock as call options on the total equity value of a company, with exercise prices based on the value thresholds at which the allocation among the various holders of a company's securities changes. Under this method, the common stock has value only if the funds available for distribution to stockholders exceeded the value of the preferred stock liquidation preference at the time of the liquidity event, such as a strategic sale or a merger. The PWERM is a scenario-based methodology that estimates the fair value of common stock based upon an analysis of future values for the company, assuming various outcomes. The common stock value is based on the probability-weighted present value of expected future investment returns considering each of the possible outcomes available as well as the rights of each

class of stock. The future value of the common stock under each outcome is discounted back to the valuation date at an appropriate risk-adjusted discount rate and probability weighted to arrive at an indication of value for the common stock. These third-party valuations were performed at various dates, which resulted in valuations of our common stock of $0.92 per share as of May 31, 2016, $1.01 per share as of October 2, 2017, $3.18 per share as of December 31, 2018 and $10.95 per share as of July 15, 2019.

In addition to considering the results of these third-party valuations, our board of directors considered various objective and subjective factors to determine the fair value of our common stock as of each grant date, including:

- the prices at which we sold shares of preferred stock and the superior rights and preferences of the preferred stock relative to our common stock at the time of each grant;
- the progress of our research and development programs, including the status and results of preclinical studies and clinical trials for our product candidates;
- our stage of development and commercialization and our business strategy;
- external market conditions affecting the biopharmaceutical industry and trends within the biopharmaceutical industry;
- our financial position, including cash on hand, and our historical and forecasted performance and operating results;
- the lack of an active public market for our common stock and our preferred stock;
- the likelihood of achieving a liquidity event, such as an initial public offering, or IPO, or sale of our company in light of prevailing market conditions; and
- the analysis of IPOs and the market performance of similar companies in the biopharmaceutical industry.

The assumptions underlying these valuations represented management's best estimate, which involved inherent uncertainties and the application of management's judgment. As a result, if we had used significantly different assumptions or estimates, the fair value of our common stock and our stock-based compensation expense could have been materially different.

Income taxes

We account for income taxes using the asset and liability method, which requires the recognition of deferred tax assets and liabilities for the expected future tax consequences of events that have been recognized in the consolidated financial statements or in our tax returns. Under this method, deferred tax assets and liabilities are determined based on differences between the financial statement carrying amounts and the tax bases of the assets and liabilities using the enacted tax rates in effect in the years in which the differences are expected to reverse. A valuation allowance against deferred tax assets is recorded if, based on the weight of the available evidence, it is more likely than not that some or all of the deferred tax assets will not be realized. Potential for recovery of deferred tax assets is evaluated by considering several factors, including estimating the future taxable profits expected, estimating future reversals of existing taxable temporary differences, considering taxable profits in carryback periods, and considering prudent and feasible tax planning strategies.

We account for uncertain tax positions using a more-likely-than-not threshold for recognizing and resolving uncertain tax positions. The evaluation of uncertain tax positions is based on factors including, but not limited to, changes in the law, the measurement of tax positions taken or expected to be taken in tax returns, the effective settlement of matters subject to audit, new audit activity, and changes in facts or circumstances related to a tax position. As of each balance sheet date, we did not have any uncertain tax positions.

Emerging growth company and smaller reporting company status

We are an emerging growth company, as defined in the JOBS Act. Under this act, emerging growth companies are permitted to delay adopting new or revised accounting standards applicable to public companies until those standards would otherwise apply to private companies. We have irrevocably elected not to avail ourselves of this exemption from new or revised accounting standards and, therefore, will be subject to the same new or revised accounting standards as other public companies that are not emerging growth companies.

We may remain classified as an EGC until the end of the fiscal year in which the fifth anniversary of our IPO occurs, although if the market value of our common stock that is held by non-affiliates exceeds $700 million as of any June 30 before that time or if we have annual gross revenues of $1.07 billion or more in any fiscal year, we would cease to be an EGC as of December 31 of the applicable year. We also would cease to be an EGC if we issue more than $1 billion of non-convertible debt over a three-year period.

We are also a "smaller reporting company," as such term is defined in Rule 12b-2 of the Exchange Act, meaning that the market value of our common stock held by non-affiliates is less than $700 million and our annual revenue is less than $100 million during the most recently completed fiscal year. We may continue to be a smaller reporting company if either (i) the market value of our common stock held by non-affiliates is less than $250 million or (ii) our annual revenue is less than $100 million during the most recently completed fiscal year and the market value of our common stock held by non-affiliates is less than $700 million. If we are a smaller reporting company at the time we cease to be an emerging growth company, we may continue to rely on exemptions from certain disclosure requirements that are available to smaller reporting companies. Specifically, as a smaller reporting company we may choose to present only the two most recent fiscal years of audited financial statements in our Annual Report on Form 10-K and, similar to emerging growth companies, smaller reporting companies have reduced disclosure obligations regarding executive compensation.

Results of operations

Comparison of the years ended December 31, 2019 and 2018

	Years ended December 31,		
	2019	2018	Change
Operating expenses:			
Research and development	$ 20,950,672	$ 14,194,732	$ 6,755,940
General and administrative	8,593,626	2,294,671	6,298,955
Total operating expenses	29,544,298	16,489,403	13,054,895
Other income (expense):			
Interest income (expense)	156,351	(182)	156,533
Foreign currency gain	1,328,140	961,316	366,824
Total other income (expense)	1,484,491	961,134	523,357
Net loss	$ (28,059,807)	$(15,528,269)	$(12,531,538)

Research and development expenses

	Years ended December 31,		
	2019	2018	Change
APR-246	$ 15,937,442	$10,957,970	$ 4,979,472
Other early-stage development programs	1,829,776	656,692	1,173,084
Unallocated research and development expenses	3,183,454	2,580,070	603,384
Total research and development expenses	$ 20,950,672	$14,194,732	$ 6,755,940

Research and development expenses for the year ended December 31, 2019 were $21.0 million, compared to $14.2 million for the year ended December 31, 2018. The increase of $6.8 million was primarily related to the advancement of our clinical product candidate APR-246. In the first quarter of 2019 we commenced a pivotal Phase 3 clinical trial of APR-246 with azacitidine for frontline treatment of *TP53* mutant MDS which is supported by two ongoing Phase 1b/2

investigator initiated trials, one in the U.S. and one in France, testing APR-246 with azacitidine as frontline treatment in *TP53* mutant MDS and AML patients.

General and administrative expenses

General and administrative expenses for the year ended December 31, 2019 were $8.6 million, compared to $2.3 million for the year ended December 31, 2018. The increase of $6.3 million was primarily related to increases of $3.4 million in legal and accounting fees, $0.3 million in consulting fees and $1.9 million in personnel related costs including $1.0 million of non-cash stock-based compensation. The increase in legal, accounting and consulting fees was primarily related to costs associated with the corporate reorganization that was completed in September 2019 as well as the preparation of our financial statements and overall readiness to become a public company. The increase in personnel costs was primarily related to increased non-cash stock-based compensation expense as a result of the addition of a member of senior management in August 2019.

Other income and expense

Foreign currency gain for the year ended December 31, 2019 was $1.3 million compared to $0.9 million for the year ended December 31, 2018. The increase of $0.4 million was primarily due to a strengthening of the U.S. dollar against the Swedish Krona during the year ended December 31, 2019. Interest income (expense) for the year ended December 31, 2019 consisted primarily of interest expense associated with our facility leases and interest income on our cash and cash equivalents. Interest expense for the year ended December 31, 2018 consisted of an insignificant amount of banking charges or fees.

Comparison of the years ended December 31, 2018 and 2017

	Years ended December 31,		
	2018	2017	Change
Operating expenses:			
Research and development	$ 14,194,732	$ 13,392,631	$ 802,101
General and administrative	2,294,671	2,459,744	(165,073)
Total operating expenses	16,489,403	15,852,375	637,028
Other income (expense):			
Interest expense	(182)	(15)	(167)
Foreign currency gain	961,316	662,140	299,176
Total other income (expense)	961,134	662,125	299,009
Net loss	$(15,528,269)	$(15,190,250)	$(338,019)

Research and development expenses

	Years ended December 31,		
	2018	2017	Change
APR-246	$10,957,970	$ 9,388,373	$1,569,597
Other early-stage development programs	656,692	1,243,991	(587,299)
Unallocated research and development expenses	2,580,070	2,760,267	(180,197)
Total research and development expenses	$14,194,732	$13,392,631	$ 802,101

Research and development expenses for the year ended December 31, 2018 were $14.2 million, compared to $13.4 million for the year ended December 31, 2017. The increase of $0.8 million was primarily related to the advancement of our clinical product candidate APR-246.

General and administrative expenses

General and administrative expenses for the year ended December 31, 2018 were $2.3 million, compared to $2.5 million for the year ended December 31, 2018.

Other income and expense

Other income and expense for the year ended December 31, 2018 consisted of an insignificant amount of banking fees on our cash balances and a foreign currency gain of $1.0 million. Other income and expense for the year ended December 31, 2017 consisted of an insignificant amount of banking charges or fees and a foreign currency gain of $0.7 million.

Liquidity and capital resources

Since our inception, we have incurred significant losses on an aggregate basis. We have not yet commercialized any of our product candidates, which are in various phases of preclinical and clinical development, and we do not expect to generate revenue from sales of any products for several years, if at all. To date, we have financed our operations through private placements of our preferred and common stock and the net proceeds received from the initial public offering (IPO) of our common stock. Through December 31, 2019, we had received net proceeds of $223.8 million from our sales of preferred and common stock. As of December 31, 2019, we had cash and cash equivalents of $130.1 million.

Cash flows

The following table summarizes our sources and uses of cash for each of the periods presented:

	Years ended December 31,		
	2019	2018	2017
Net cash provided by (used in):			
Operating activities	$(26,708,707)	$(15,250,234)	$(14,002,118)
Investing activities	(30,901)	(3,702)	—
Financing activities	92,575,538	56,366,742	23,343,863
Net increase in cash and cash equivalents	$ 65,835,930	$ 41,112,806	$ 9,341,745

Operating activities

Cash used in operating activities resulted primarily from our net losses adjusted for non-cash charges and changes in components of working capital. Net cash used in operating activities was $26.7 million for the year ended December 31, 2019 compared to $15.3 million for the year ended December 31, 2018. The increase in cash used in operating activities of $11.5 million was primarily attributable to an increase in our net loss of $12.5 million, resulting from both increased research and development expenses and increased general and administrative expenses discussed previously.

Net cash used in operating activities was $15.3 million for the year ended December 31, 2018 compared to $14.0 million for the year ended December 31, 2017. The increase in cash used in operating activities of $1.3 million was primarily attributable to an increase in our net loss of $0.3 million, an increase in non-cash expenses of $0.4 million, resulting primarily from an increase in foreign currency gains of $0.3 million and a decreases in stock-based compensation of $0.1 million, and a decrease in the components of working capital of $0.5 million.

Investing activities

Cash used in investing activities for the years ended December 31, 2019, 2018 and 2017 was $30,901, $3,702 and $0, respectively. Cash used in investing activities for these years represented the acquisition and property and equipment

We expect that investing activities will increase over the next several years.

Financing activities

Net cash provided by financing activities was $92.6 million for the year ended December 31, 2019 compared to $56.4 million for the year ended December 31, 2018. The increase in cash provided by financing activities of $36.2 million was primarily attributable to net proceeds of $86.9 million received from our IPO which was completed in October 2019 and net proceeds of $5.6 million from the issuance of Series C convertible preferred stock in February 2019.

Net cash provided by financing activities was $56.4 million for the year ended December 31, 2018 compared to $23.3 million for the year ended December 31, 2017. The increase in cash provided by financing activities of $33.1 million was attributable to the issuance of Series C convertible preferred stock in November 2018 for net proceeds of $56.4 million. In October 2017, we issued Series B convertible preferred stock for net proceeds of $23.3 million.

Funding requirements

We expect our expenses to increase substantially in connection with our ongoing development activities related to APR-246 and other product candidates and programs which are still in the early stages of clinical development. In addition, we have incurred and continue to incur additional costs associated with operating as a public company. We expect that our expenses will increase substantially if and as we:

- conduct our current and future clinical trials and additional preclinical research of APR-246;
- initiate and continue research and preclinical and clinical development of our other product candidates;
- seek to identify and develop additional product candidates;
- seek marketing approvals for any of our product candidates that successfully complete clinical trials, if any;
- establish a sales, marketing, manufacturing and distribution infrastructure to commercialize any products for which we may obtain marketing approval;
- require the manufacture of larger quantities of our product candidates for clinical development and potentially commercialization;
- maintain, expand, protect and enforce our intellectual property portfolio;
- acquire or in-license other drugs and technologies;
- defend against any claims of infringement, misappropriation or other violation of third-party intellectual property;
- hire and retain additional clinical, quality control and scientific personnel;
- build out new facilities or expand existing facilities to support our ongoing development activity;
- add operational, financial and management information systems and personnel, including personnel to support our drug development, any future commercialization efforts and our transition to a public company; and

- continue to operate as a public company.

As of December 31, 2019, we had cash and cash equivalents of $130.1 million. We believe that our existing cash and cash equivalents, will enable us to fund our operating expenses and capital expenditure requirements into 2023. We have based this estimate on assumptions that may prove to be wrong, and we could exhaust our available capital resources sooner than we expect.

Because of the numerous risks and uncertainties associated with the development of APR-246 and other product candidates and programs and because the extent to which we may enter into collaborations with third parties for development of our product candidates is unknown, we are unable to estimate the timing and amounts of increased capital outlays and operating expenses associated with completing the research and development of our product candidates. Our future capital requirements will depend on many factors, including:

- the scope, progress, results and costs of our current and future clinical trials of APR-246 for our current targeted indications;

- the scope, progress, results and costs of drug discovery, preclinical research and clinical trials for APR-246 and our other product candidates;

- the number of future product candidates that we pursue and their development requirements;

- the costs, timing and outcome of regulatory review of our product candidates;

- the extent to which we acquire or invest in businesses, products and technologies, including entering into or maintaining licensing or collaboration arrangements for product candidates on favorable terms, although we currently have no commitments or agreements to complete any such transactions;

- the costs and timing of future commercialization activities, including drug sales, marketing, manufacturing and distribution, for any of our product candidates for which we receive marketing approval, to the extent that such sales, marketing, manufacturing and distribution are not the responsibility of any collaborator that we may have at such time;

- the amount of revenue, if any, received from commercial sales of our product candidates, should any of our product candidates receive marketing approval;

- the costs of preparing, filing and prosecuting patent applications, maintaining, protecting and enforcing our intellectual property rights and defending intellectual property-related claims;

- our headcount growth and associated costs as we expand our business operations and our research and development activities; and

- the costs of operating as a public company.

Developing drug products, including conducting preclinical studies and clinical trials, is a time-consuming, expensive and uncertain process that takes years to complete, and we may never generate the necessary data or results required to obtain marketing approval for any product candidates or generate revenue from the sale of any products for which we may obtain marketing approval. In addition, our product candidates, if approved, may not achieve commercial success. Our commercial revenues, if any, will be derived from sales of drugs that we do not expect to be commercially available for many years, if ever. Accordingly, we will need to obtain substantial additional funds to achieve our business objectives.

Adequate additional funds may not be available to us on acceptable terms, or at all. We do not currently have any committed external source of funds. To the extent that we raise additional capital through the sale of equity or

convertible debt securities, ownership interests in our securities may be diluted, and the terms of these securities may include liquidation or other preferences and anti-dilution protections that could adversely affect the rights of our common stockholders. Additional debt or preferred equity financing, if available, may involve agreements that include restrictive covenants that may limit our ability to take specific actions, such as incurring debt, making capital expenditures or declaring dividends, which could adversely impact our ability to conduct our business, and may require the issuance of warrants, which could potentially dilute existing ownership interest.

If we raise additional funds through collaborations, strategic alliances or licensing arrangements with third parties, we may have to relinquish valuable rights to our technology, future revenue streams, research programs, or product candidates or grant licenses on terms that may not be favorable to us. If we are unable to raise additional funds through equity or debt financings or collaborations, strategic alliances or licensing arrangements with third parties when needed, we may be required to delay, limit, reduce and/or terminate our product development programs or any future commercialization efforts or grant rights to develop and market product candidates that we would otherwise prefer to develop and market ourselves.

Contractual obligations and commitments

The following table summarizes our contractual obligations at December 31, 2019:

	Payments due by period				
	Total	Less than 1 year	1 - 3 years	3 - 5 years	More than 5 years
Operating leases(1)	$567,850	$ 251,008	$316,842	$ —	$ —
Total	$567,850	$ 251,008	$316,842	$ —	$ —

(1) Represents minimum payments due for our lease of office space in Boston, Massachusetts under an operating lease agreement that, as amended, expires in 2021 and our lease of office and laboratory space in Solna, Sweden under an operating lease agreement that expires in June 2022.

We enter into contracts in the normal course of business with CROs and CMOs for clinical trials, preclinical research studies and testing, manufacturing and other services and products for operating purposes. These contracts do not contain any minimum purchase commitments and are cancelable by us upon prior notice of 30 days and, as a result, are not included in the table of contractual obligations above. Payments due upon cancelation consist only of payments for services provided and expenses incurred up to the date of cancelation.

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 in the rules and regulations of the SEC.

Recent accounting pronouncements

See Note 2 to our consolidated financial statements that discusses new accounting pronouncements

Item 7A. Quantitative and qualitative disclosures about market risk

Interest Rate Risk

We are exposed to market risk related changes in interest rates. As of December 31, 2019, our cash equivalents consisted of bank deposits and money market accounts. Our primary exposure to market risk is interest income sensitivity, which is affected by changes in the general level of U.S. interest rates. However, historical fluctuations in interest income have not been significant for us.

Foreign Currency Exchange Rate Risk

We face market risk to the extent that changes in foreign currency exchange rates affect our non-U.S. dollar functional currency foreign subsidiaries' revenues, expenses, assets and liabilities. The financial position and results of operations of our subsidiaries Aprea AB and Aprea Personal AB are measured using the foreign subsidiaries' local currency as the functional currency. Aprea AB cash accounts holding U.S. dollars are remeasured based upon the exchange rate at the date of remeasurement with the resulting gain or loss included in the consolidated statement of operations and comprehensive loss.

Our investments in foreign subsidiaries with a functional currency other than the U.S. dollar are generally considered long-term. In addition, we do not believe that we currently have any significant direct foreign exchange risk. Accordingly, we have not used any derivative financial instruments to hedge exposure to such risk.

Item 8. Financial Statements and Supplementary Data

Aprea Therapeutics, Inc.
Index to Consolidated Financial Statements

Report of Independent Registered Public Accounting Firm

To the Stockholders and the Board of Directors of Aprea Therapeutics, Inc.

Opinion on the Financial Statements

We have audited the accompanying consolidated balance sheet of Aprea Therapeutics, Inc. (the Company) as of December 31, 2019, the related consolidated statements of operations and comprehensive loss, convertible preferred stock and stockholders' equity (deficit) and cash flows for the year then ended, 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 consolidated financial position of the Company at December 31, 2019, and the consolidated results of its operations and its cash flows for the year then ended, in conformity with U.S. generally accepted accounting principles.

Adoption of ASU No. 2016-02

As discussed in Note 2 to the consolidated financial statements, the Company changed its method of accounting for leases in 2019 due to the adoption of Accounting Standards Update (ASU) No. 2016-02, Leases (Topic 842), 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 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 the financial statements are free of material misstatement, whether due to error or fraud. The Company is not required to have, nor were we engaged to perform, an audit of its internal control over financial reporting. As part of our audit we are required to obtain an understanding of internal control over financial reporting but not for the purpose of expressing an opinion on the effectiveness of the Company's internal control over financial reporting. Accordingly, we express no such opinion.

Our audit 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 included 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 audit provides a reasonable basis for our opinion.

/s/ Ernst & Young LLP

We have served as the Company's auditor since 2019.

Iselin, New Jersey
March 27, 2020

Report of Independent Registered Public Accounting Firm

To the Stockholders and the Board of Directors of Aprea Therapeutics AB

Opinion on the Financial Statements

We have audited the accompanying consolidated balance sheet of Aprea Therapeutics AB (the Company) as of December 31, 2018, the related consolidated statements of operations and comprehensive loss, convertible preferred stock and stockholders' equity (deficit) and cash flows for each of the two 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 the results of its operations and its cash flows for each of the two years in the period ended December 31, 2018, in conformity with U.S. generally accepted accounting principles.

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 Public Company Accounting Oversight Board (United States) (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. The Company is not required to have, nor were we engaged to perform, an audit of its internal control over financial reporting. As part of our audits we are required to obtain an understanding of internal control over financial reporting but not for the purpose of expressing an opinion on the effectiveness of the Company's internal control over financial reporting. Accordingly, we express no such opinion.

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 included 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 AB

We have served as the Company's auditor since 2015.

Stockholm, Sweden
August 20, 2019
Except for the stock split described in Note 2, as to which the date is September 27, 2019

Aprea Therapeutics, Inc.
Consolidated Balance Sheets

	December 31, 2019	December 31, 2018
Assets		
Current assets:		
Cash and cash equivalents	$ 130,088,869	$ 65,675,931
Prepaid expenses and other current assets	2,955,878	322,146
Total current assets	133,044,747	65,998,077
Property and equipment, net	41,639	24,450
Right of use lease asset	521,392	—
Other noncurrent assets	107	111
Total assets	$ 133,607,885	$ 66,022,638
Liabilities, Convertible Preferred Stock and Stockholders' Equity (Deficit)		
Current liabilities:		
Accounts payable	$ 2,176,852	$ 1,739,337
Accrued expenses	6,642,553	3,128,772
Lease liability—current	242,329	—
Total current liabilities	9,061,734	4,868,109
Lease liability—noncurrent	302,621	—
Total liabilities	9,364,355	4,868,109
Commitments and contingencies (Note 11)		
Convertible preferred stock:		
Series A convertible preferred stock, $0.001 par value; 0 shares issued and outstanding at December 31, 2019 and 612,446 shares issued and outstanding at December 31, 2018	—	6,483,044
Series B convertible preferred stock, $0.001 par value; 0 shares issued and outstanding at December 31, 2019 and 7,235,969 shares issued and outstanding at December 31, 2018	—	49,742,942
Series C convertible preferred stock, $0.001 par value; 0 shares issued and outstanding at December 31, 2019 and 4,712,698 issued and outstanding at December 31, 2018	—	56,364,645
Total convertible preferred stock	—	112,590,631
Stockholders' equity (deficit):		
Common stock, $0.001 par value at December 31, 2019 and $0.11 par value at December 31, 2018; 21,022,752 and 1,155,366 shares issued and outstanding at December 31, 2019 and 2018, respectively.	21,023	127,091
Additional paid-in capital	226,284,548	19,666,588
Accumulated other comprehensive loss	(11,533,778)	(8,761,325)
Accumulated deficit	(90,528,263)	(62,468,456)
Total stockholders' equity (deficit)	124,243,530	(51,436,102)
Total liabilities, convertible preferred stock and stockholders' equity (deficit)	$ 133,607,885	$ 66,022,638

See accompanying notes to consolidated financial statements.

Aprea Therapeutics, Inc.
Consolidated Statements of Operations and Comprehensive Loss

	Year Ended December 31,		
	2019	2018	2017
Operating expenses:			
Research and development	$ 20,950,672	$ 14,194,732	$ 13,392,631
General and administrative	8,593,626	2,294,671	2,459,744
Total operating expenses	29,544,298	16,489,403	15,852,375
Other income (expense):			
Interest income (expense)	156,351	(182)	(15)
Foreign currency gain	1,328,140	961,316	662,140
Total other income (expense)	1,484,491	961,134	662,125
Net loss	$ (28,059,807)	$ (15,528,269)	$ (15,190,250)
Other comprehensive income (loss):			
Foreign currency translation	(2,772,453)	(473,919)	495,160
Total comprehensive loss	$ (30,832,260)	$ (16,002,188)	$ (14,695,090)
Net loss per share attributable to common stockholders, basic and diluted	$ (4.67)	$ (13.45)	$ (13.17)
Weighted-average common shares outstanding, basic and diluted	6,002,486	1,154,368	1,153,069

See accompanying notes to consolidated financial statements

Aprea Therapeutics, Inc.
Consolidated Statements of Convertible Preferred Stock and Stockholders' Equity (Deficit)

	Convertible preferred stock											
	Series A		Series B		Series C		Common Stock		Additional Paid-in capital	Accumulated other comprehensive loss	Accumulated deficit	Total stockholders' equity (deficit)
	Shares	Amount	Shares	Amount	Shares	Amount	Shares	Amount				
Balance at January 1, 2017	612,446	$ 6,483,044	3,913,207	$ 26,399,079	—	$ —	1,153,061	$ 126,838	$ 18,940,120	$ (8,782,566)	$ (31,749,937)	$ (21,465,545)
Issuance of Series B convertible preferred stock, net of issuance costs of $47,047	—	—	3,322,762	23,343,863	—	—	—	—	—	—	—	—
Stock-based compensation	—	—	—	—	—	—	—	—	395,440	—	—	395,440
Foreign currency translation	—	—	—	—	—	—	—	—	—	495,160	—	495,160
Net loss	—	—	—	—	—	—	—	—	—	—	(15,190,250)	(15,190,250)
Balance at December 31, 2017	612,446	$ 6,483,044	7,235,969	$ 49,742,942	—	$ —	1,153,061	$ 126,838	$ 19,335,560	$ (8,287,406)	$ (46,940,187)	$ (35,765,195)
Issuance of Series C convertible preferred stock, net of issuance costs of $3,278,302	—	—	—	—	4,712,698	56,364,645	—	—	—	—	—	—
Exercise of stock options	—	—	—	—	—	—	2,305	253	1,844	—	—	2,097
Stock-based compensation	—	—	—	—	—	—	—	—	329,184	—	—	329,184
Foreign currency translation	—	—	—	—	—	—	—	—	—	(473,919)	—	(473,919)
Net loss	—	—	—	—	—	—	—	—	—	—	(15,528,269)	(15,528,269)
Balance at December 31, 2018	612,446	$ 6,483,044	7,235,969	$ 49,742,942	4,712,698	$ 56,364,645	1,155,366	$ 127,091	$ 19,666,588	$ (8,761,325)	$ (62,468,456)	$ (51,436,102)
Issuance of Series C convertible preferred stock, net of issuance costs of $53,509	—	—	—	—	467,179	5,598,362	—	—	—	—	—	—
Issuance of common stock	—	—	—	—	—	—	160	—	100	—	—	100
Exercise of stock options	—	—	—	—	—	—	322,267	3,179	67,818	—	—	70,997
Stock-based compensation	—	—	—	—	—	—	—	—	1,345,722	—	—	1,345,722
Foreign currency translation	—	—	—	—	—	—	—	—	—	(2,772,453)	—	(2,772,453)
Exchange of preferred and common stock of Aprea Therapeutics AB into stock of Aprea Therapeutics, Inc.	—	—	—	—	—	—	—	(128,792)	128,792	—	—	—
Conversion of preferred stock into common stock	(612,446)	(6,483,044)	(7,235,969)	(49,742,942)	(5,179,877)	(61,963,007)	13,028,292	13,028	118,175,965	—	—	118,188,993
Common stock issued in IPO, net of issuance costs of $10,843,925	—	—	—	—	—	—	6,516,667	6,517	86,899,563	—	—	86,906,080
Net loss	—	—	—	—	—	—	—	—	—	—	(28,059,807)	(28,059,807)
Balance at December 31, 2019	—	$ —	—	$ —	—	$ —	21,022,752	$ 21,023	$ 226,284,548	$ (11,533,778)	$ (90,528,263)	$ 124,243,530

See accompanying notes to consolidated financial statements.

Aprea Therapeutics, Inc.
Consolidated Statements of Cash Flows

	Years ended December 31,		
	2019	2018	2017
Cash flows from operating activities:			
Net loss	$ (28,059,807)	$ (15,528,269)	$ (15,190,250)
Adjustments to reconcile net loss to net cash used in operating activities:			
Depreciation and amortization	11,126	8,316	7,932
Stock-based compensation	1,345,722	329,184	395,440
Amortization of right of use lease asset	159,128	—	—
Foreign currency gain	(1,328,140)	(961,316)	(662,140)
Changes in operating assets and liabilities:			
Prepaid expense and other current assets	(2,633,732)	(19,452)	4,041
Accounts payable	437,515	214,380	327,054
Accrued expenses and other liabilities	3,513,782	706,923	1,115,805
Lease liability	(154,301)	—	—
Net cash used in operating activities	(26,708,707)	(15,250,234)	(14,002,118)
Cash flows from investing activities:			
Purchases of property and equipment	(30,901)	(3,702)	—
Net cash used in investing activities	(30,901)	(3,702)	—
Cash flows from financing activities:			
Proceeds from the exercise of stock options	70,997	2,097	—
Proceeds from issuance of common stock in initial public offering, net	86,906,179	—	—
Proceeds from issuance of Series B convertible preferred, net	—	—	23,343,863
Proceeds from issuance of Series C convertible preferred, net	5,598,362	56,364,645	—
Net cash provided by financing activities	92,575,538	56,366,742	23,343,863
Increase in cash	65,835,930	41,112,806	9,341,745
Effect of exchange rate changes on cash	(1,422,992)	161,637	1,394,568
Cash and cash equivalents—beginning of year	65,675,931	24,401,488	13,665,175
Cash and cash equivalents—end of year	$ 130,088,869	$ 65,675,931	$ 24,401,488

See accompanying notes to consolidated financial statements.

Aprea Therapeutics, Inc.
Notes to Consolidated Financial Statements

1. Nature of business and basis of presentation

Nature of business—Aprea Therapeutics, Inc. (or the "Company") is a clinical-stage biopharmaceutical company focused on developing and commercializing novel cancer therapeutics that reactivate mutant tumor suppressor protein p53. p53 is the protein expressed from the *TP53* gene, the most commonly mutated gene in cancer. The Company began principal operations in 2006 and is headquartered in Boston, Massachusetts with research facilities in Stockholm, Sweden.

Corporate reorganization - In September 2019, the Company completed a corporate reorganization whereby Aprea Therapeutics AB became a wholly-owned subsidiary of the Company. In connection with the corporate reorganization, each issued and outstanding share of Series A, Series B and Series C convertible preferred stock of Aprea Therapeutics AB was exchanged on a one for one basis into shares of Series A, Series B and Series C convertible preferred stock of the Company.

Each share of common stock of Aprea Therapeutics AB ($0.11 par value) was also exchanged on a one for one basis into shares of common stock of the Company ($0.001 par value).

Basis of presentation and management plans—The accompanying financial statements are prepared in conformity with accounting principles generally accepted in the United States ("U.S. GAAP"). The accompanying financial statements have been prepared on a going concern basis, which contemplates the realization of assets and the satisfaction of liabilities in the normal course of business.

Since its inception, the Company has devoted substantially all of its efforts to business planning, research and development, recruiting management and technical staff, and raising capital, and has financed its operations through the issuance of convertible preferred stock and common stock.

The Company is subject to risks common to companies in the biopharmaceutical industry. There can be no assurance that the Company's research and development will be successfully completed, that adequate protection for the Company's intellectual property will be maintained, that any therapeutic products developed will obtain required regulatory approval or that any approved or consumer products will be commercially viable. Even if the Company's development efforts are successful, it is uncertain when, if ever, the Company will generate significant product sales.

The Company believes that the December 31, 2019 cash balance of $130,088,869 will be sufficient to fund the Company's operations into 2023. In the event that additional funds are not available thereafter, management would expect to significantly reduce expenditures to conserve cash, which would involve scaling back or curtailing new development activity.

2. Summary of significant accounting policies

Principles of consolidation—The consolidated financial statements include the accounts of the Company and its wholly owned subsidiaries Aprea Therapeutics AB, Aprea Personal AB, which was incorporated in May 2009, and Aprea US, Inc., which was incorporated in June 2016. Management has concluded it has a single reporting segment for purposes of reporting financial condition and results of operations. All intercompany transactions and balances have been eliminated.

Use of estimates— The preparation of financial statements in conformity with U.S. GAAP requires management to make estimates and assumptions that affect the reported amounts of assets, liabilities, revenue, and expenses as of and during the reporting period. The Company bases estimates and assumptions on historical experience when available and on various factors that it believes to be reasonable under the circumstances. The Company assesses estimates on an ongoing basis; however, actual results could materially differ from those estimates. Significant items subject to such estimates and assumptions include fair value of stock-based compensation expense.

Aprea Therapeutics, Inc.
Notes to Consolidated Financial Statements (continued)

Stock split—In September 2019, the Company effected a 1-for-1.6045 stock split of the Company's preferred and common stock. All share and per share amounts of preferred and common stock contained in the Company's consolidated financial statements have been retroactively adjusted for all periods presented to give effect to the stock split.

Foreign currency and currency translation— The functional currency for Aprea Therapeutics AB and its wholly owned foreign subsidiary, Aprea Personal AB, is the Swedish Krona. Assets and liabilities of Aprea Therapeutics AB and Aprea Personal AB are translated into United States dollars at the exchange rate in effect on the balance sheet date. Revenues and expenses are translated at the average exchange rate in effect during the period. Unrealized translation gains and losses are recorded as a cumulative translation adjustment, which is included in the consolidated statements of convertible preferred stock and stockholders' equity (deficit) as a component of accumulated other comprehensive loss. Adjustments that arise from exchange rate changes on transactions denominated in a currency other than the local currency are included in other income (expense), net in the consolidated statements of operations as incurred.

Concentrations of credit risk—Financial instruments that potentially subject the Company to significant concentration of credit risk consist primarily of cash. Periodically, the Company may maintain deposits in financial institutions in excess of government insured limits. Management believes that the Company is not exposed to significant credit risk as the Company's deposits are held at financial institutions that management believes to be of high credit quality, and the Company has not experienced any losses on these deposits.

Cash and cash equivalents—The Company considers all highly liquid investments with original maturities of three months or less at the date of purchase to be cash equivalents.

Property and equipment—Property and equipment are recorded at cost. Expenditures for repairs and maintenance are expensed as incurred. When assets are retired or disposed of, the assets and related accumulated depreciation are eliminated from the accounts, and any resulting gain or loss is included in the determination of net income or loss. Fixed assets acquired for research and development purposes are assessed for alternative future use. Depreciation is provided using the straight-line method over the estimated useful lives of the related assets. Leasehold improvements are amortized over the shorter of the lease term or the estimated useful life of the asset.

Asset category	Estimated useful life
Computer equipment and software	5 years
Furniture and fixtures	5 years
Laboratory equipment and office furniture	5 years
Leasehold improvements	Remainder of lease term

Impairment of long-lived assets—Periodically, the Company evaluates its long-lived assets, which consist primarily of property and equipment, for impairment whenever events or changes in circumstances indicate that the carrying amount of such assets may not be recoverable. Recoverability of assets to be held and used is measured by a comparison of the carrying amount of an asset to the future undiscounted net cash flows expected to be generated by the asset. If such assets are considered to be impaired, the impairment to be recognized is measured by the amount by which the carrying amount of the asset exceeds the fair value of the asset. To date, no impairments have occurred.

Fair value of financial instruments—The accounting standard for fair value measurements provides a framework for measuring fair value and requires expanded disclosures regarding fair value measurements. Fair value is defined as the price that would be received upon sale of an asset or paid to transfer a liability between market participants at measurement dates. ASC Topic 820, Fair Value Measurement ("ASC 820"), establishes a three-level valuation hierarchy for instruments measured at fair value. The hierarchy is based on the transparency of inputs to the valuation of an asset or liability as of the measurement date. The hierarchy defines three levels of valuation inputs, of which the first two are considered observable and the last is considered unobservable:

- Level 1 inputs: Quoted prices in active markets for identical assets or liabilities.

- Level 2 inputs: Inputs other than quoted prices included within Level 1 that are either directly or indirectly observable, such as quoted market prices, interest rates and yield curves.

- Level 3 inputs: Unobservable inputs developed using estimates or assumptions developed by the Company, which reflect those that a market participant would use in pricing the asset or liability.

To the extent that the valuation is based on models or inputs that are less observable or unobservable in the market, the determination of fair value requires more judgment. Accordingly, the degree of judgment exercised by the Company in determining fair value is greatest for instruments categorized in Level 3. A financial instrument's level within the fair value hierarchy is based on the lowest level of any input that is significant to the fair value measurement.

The Company's financial instruments consist of accounts payable. The carrying amount of accounts payable is considered a reasonable estimate of fair value due to the short-term maturity.

Convertible preferred stock— The Company has classified convertible preferred stock as temporary equity in the accompanying December 31, 2018 balance sheet due to certain change in control events that are outside of the Company's control, including sale or transfer of control of the Company, as holders of the Preferred Stock could cause redemption of the shares in these situations. The Company does not accrete the carrying values of the Preferred Stock to the redemption values since a liquidation event was not considered probable as of December 31, 2018. Subsequent adjustments of the carrying values to the ultimate redemption values will be made only if it becomes probable that such a liquidation event will occur.

Accounting for leases—In February 2016, the Financial Accounting Standards Board ("FASB") issued Accounting Standards Update ("ASU") No. 2016 02, "Leases" ("ASC 842") to enhance the transparency and comparability of financial reporting related to leasing arrangements. Under this new lease standard, most leases are required to be recognized on the balance sheet as right-of-use assets and lease liabilities. Disclosure requirements have been enhanced with the objective of enabling financial statement users to assess the amount, timing, and uncertainty of cash flows arising from leases. Prior to January 1, 2019, GAAP did not require lessees to recognize assets and liabilities related to operating leases on the balance sheet. The new standard establishes a right-of-use ("ROU") model that requires a lessee to recognize a ROU asset and corresponding lease liability on the balance sheet for all leases with a term longer than 12 months. Leases will be classified as finance or operating, with classification affecting the pattern and classification of expense recognition in the income statement as well as the reduction of the right of use asset.

The Company has adopted the standard effective January 1, 2019, using the modified retrospective method. The new standard provides a number of optional practical expedients in transition. The Company has elected to apply the 'package of practical expedients' which allow us to not reassess (i) whether existing or expired arrangements contain a lease, (ii) the lease classification of existing or expired leases, or (iii) whether previous initial direct costs would qualify for capitalization under the new lease standard. The Company has also elected to apply (i) the practical expedient which allows us to not separate lease and non-lease components, for new leases entered into after adoption and (ii) the short-term lease exemption for all leases with an original term of less than 12 months, for purposes of applying the recognition and measurements requirements in the new standard. For the impact to the Company's consolidated financial statement upon adoption of the new leasing standard, see Note 3 to our unaudited condensed consolidated financial statements.

At the inception of an arrangement, the Company determines whether the arrangement is or contains a lease based on specific facts and circumstances, the existence of an identified asset(s), if any, and the Company's control over the use of the identified asset(s), if applicable. Operating lease liabilities and their corresponding right-of-use assets are recorded based on the present value of future lease payments over the expected lease term. The interest rate implicit in lease contracts is typically not readily determinable. As such, the Company will utilize the incremental borrowing rate, which is the rate incurred to borrow on a collateralized basis over a similar term an amount equal to the lease payments in a similar economic environment. As of the ASC 842 effective date, the Company's incremental borrowing rate ranged from approximately 3.0% to 4.3% based on the remaining lease term of the applicable leases.

The Company has elected not to separate lease and non-lease components as a single component. Operating leases are recognized on the balance sheet as ROU lease assets, lease liabilities current and lease liabilities non-current. Fixed rents are included in the calculation of the lease balances while variable costs paid for certain operating and pass-through costs are excluded. Lease expense is recognized over the expected term on a straight-line basis.

Research and development costs—Research and development costs are charged to expense as incurred. Research and development expenses incurred in performing research and development activities, include salaries and benefits, materials and supplies, preclinical expenses, stock-based compensation expense, depreciation of equipment, contract services, and other outside expenses. Costs for certain development activities are recognized based on an evaluation of the progress to completion of specific tasks using or information provided to the Company by its vendors on their actual costs incurred. Payments for these activities are based on the terms of the individual arrangements, which may differ from the pattern of costs incurred, and are reflected in the financial statements as prepaid or accrued research and development.

Stock-based compensation—The Company measures stock options and other stock-based awards granted to employees and directors based on their fair value on the date of the grant and recognize compensation expense of those awards, net of estimated forfeitures, over the requisite service period, which is generally the vesting period of the respective award. The Company applies the straight-line method of expense recognition to all awards with only service based vesting conditions.

For stock-based awards granted to non-employees, compensation expense is recognized over the period during which services are rendered by such non-employees until completed in accordance with the FASB issued ASU No. 2018-07, Compensation Stock Compensation (Topic 718): Improvements to Nonemployee Share Based Payment Accounting. The new standard largely aligns the accounting for share based payment awards issued to employees and nonemployees by expanding the scope of ASC 718 to apply to nonemployee share based transactions, as long as the transaction is not effectively a form of financing.

The Company estimates the fair value of each stock option grant on the date of grant using the Black Scholes option pricing model, which uses as inputs the fair value of the Company's common stock and assumptions the Company makes for the volatility of its common stock, the expected term of its stock options, the risk free interest rate for a period that approximates the expected term of its stock options and its expected dividend yield.

Determination of Fair Value of Common Stock

Prior to the completion of the Company's IPO, there had been no public market for the Company's common stock, the estimated fair value of its common stock had been determined by its board of directors as of the date of each option grant, with input from management, considering the Company's most recently available third party valuations of common stock and its board of directors' assessment of additional objective and subjective factors that it believed were relevant and which may have changed from the date of the most recent valuation through the date of the grant. These third-party valuations were performed in accordance with the guidance outlined in the American Institute of Certified Public Accountants' Accounting and Valuation Guide, Valuation of Privately Held Company Equity Securities Issued as Compensation.

The Company's common stock valuations were prepared using a hybrid method, which used market approaches to estimate its enterprise value. The hybrid method is a probability weighed expected return method, or PWERM, where the equity value in one or more scenarios is calculated using an option pricing method, or OPM. The OPM treats common stock and preferred stock as call options on the total equity value of a company, with exercise prices based on the value thresholds at which the allocation among the various holders of a company's securities changes. Under this method, the common stock has value only if the funds available for distribution to stockholders exceeded the value of the preferred stock liquidation preference at the time of the liquidity event, such as a strategic sale or a merger. The PWERM is a scenario-based methodology that estimates the fair value of common stock based upon an analysis of future values for the company, assuming various outcomes. The common stock value is based on the probability weighted present value of expected future investment returns considering each of the possible outcomes available as well

as the rights of each class of stock. The future value of the common stock under each outcome is discounted back to the valuation date at an appropriate risk adjusted discount rate and probability weighted to arrive at an indication of value for the common stock. These third party valuations were performed at various dates, which resulted in valuations of the Company's common stock of $0.92 per share as of May 31, 2016, $1.01 per share as of October 2, 2017, $3.18 per share as of December 31, 2018 and $10.95 per share as of July 15, 2019.

In addition to considering the results of these third-party valuations, the Company's board of directors considered various objective and subjective factors to determine the fair value of its common stock as of each grant date, including:

- the prices at which the Company sold shares of preferred stock and the superior rights and preferences of the preferred stock relative to its common stock at the time of each grant;
- the progress of the Company's research and development programs, including the status and results of preclinical studies and clinical trials for its product candidates;
- the Company's stage of development and commercialization and its business strategy;
- external market conditions affecting the biopharmaceutical industry and trends within the biopharmaceutical industry;
- the Company's financial position, including cash on hand, and its historical and forecasted performance and operating results;
- the lack of an active public market for the Company's common stock and its preferred stock;
- the likelihood of achieving a liquidity event, such as an IPO, or sale of the Company in light of prevailing market conditions; and
- the analysis of IPOs and the market performance of similar companies in the biopharmaceutical industry.

The assumptions underlying these valuations represented management's best estimate, which involved inherent uncertainties and the application of management's judgment. As a result, if the Company had used significantly different assumptions or estimates, the fair value of its common stock and its stock-based compensation expense could have been materially different.

Income taxes—The Company accounts for income tax in accordance with ASC 740-10, Income Taxes ("ASC 740-10"), which requires the recognition of deferred tax assets and liabilities for the expected future tax consequences of events that have been included in the Company's financial statements and tax returns. Deferred tax assets and liabilities are determined based upon the differences between the financial statement carrying amounts and the tax bases of existing assets and liabilities and for loss and credit carryforwards, using enacted tax rates expected to be in effect in the year in which the differences are expected to reverse. Deferred tax assets are reduced by a valuation allowance if it is more likely than not that these assets may not be realized. The Company determines whether it is more likely than not that a tax position will be sustained upon examination. If it is not more likely than not that a position will be sustained, none of the benefit attributable to the position is recognized. The tax benefit to be recognized for any tax position that meets the more-likely-than-not recognition threshold is calculated as the largest amount that is more than 50% likely of being realized upon resolution of the contingency. The Company accounts for interest and penalties related to uncertain tax positions as part of its provision for income taxes.

Net loss per share—The Company has reported losses since inception and has computed basic net loss per share attributable to common stockholders by dividing net loss attributable to common stockholders by the weighted-average number of common shares outstanding for the period, without consideration for potentially dilutive securities. The Company computes diluted net loss per common share after giving consideration to all potentially dilutive common

shares, including options to purchase common stock and convertible preferred stock, outstanding during the period determined using the treasury-stock and if-converted methods, except where the effect of including such securities would be antidilutive. Because the Company has reported net losses since inception, these potential common shares have been anti-dilutive and basic and diluted loss per share have been the same.

The following table sets forth the potentially dilutive securities that have been excluded from the calculation of diluted net loss per share because to include them would be anti-dilutive (in common stock equivalent shares):

	Year ended December 31,		
	2019	2018	2017
Series A convertible preferred stock	—	612,446	612,446
Series B convertible preferred stock	—	7,235,969	7,235,969
Series C convertible preferred stock	—	4,712,698	—
Options to purchase common stock	3,499,934	1,844,188	1,897,206
Total shares of common stock equivalents	3,499,934	14,405,301	9,745,621

Recently issued accounting pronouncements

From time to time, new accounting pronouncements are issued by the Financial Accounting Standards Board (“FASB”) or other standard setting bodies that the Company adopts as of the specified effective date. Unless otherwise discussed below, the Company does not believe that the adoption of recently issued standards have or may have a material impact on our consolidated financial statements or disclosures.

In June 2018, the FASB issued ASU No. 2018-07, “*Compensation—Stock Compensation*”, which expands the scope of Topic 718 to include share-based payment transactions for acquiring goods and services from nonemployees, except for specific exceptions. This ASU is effective for annual or any interim periods beginning after December 15, 2019. The Company is currently assessing the impact of adopting this authoritative guidance on its financial statements.

In June 2016, the FASB issued ASU 2016-13, Financial Instruments—Credit Losses (Topic 326): Measurement of Credit Losses on Financial Instruments ("ASU 2016-13"), which amends the impairment model by requiring entities to use a forward-looking approach based on expected losses rather than incurred losses to estimate credit losses on certain types of financial instruments, including trade receivables. ASU 2016-13 was adopted by the Company on January 1, 2020 and has no current impact on the Company as we do not have any financial instruments covered by the topic.

Management does not believe that any other recently issued, but not yet effective accounting pronouncements, if adopted, would have a material impact on the accompanying financial statements.

3. Property and equipment

Property and equipment consist of the following:

	December 31,	
	2019	2018
Lab equipment	$ 88,107	$ 69,770
Furniture & Fixtures	20,580	16,313
Computer equipment	18,399	12,689
Property and equipment, at cost	127,086	98,772
Less accumulated depreciation and amortization	(85,447)	(74,322)
Property and equipment—net	$ 41,639	$ 24,450

Depreciation expense for years ended December 31, 2019, 2018 and 2017 was $11,126, $8,316 and $7,932, respectively.

4. Fair value measurements

The Company's financial instruments consist of accounts payable. The carrying amount of accounts payable is considered a reasonable estimate of fair value due to the short-term maturity.

The accounting standard for fair value measurements provides a framework for measuring fair value and requires expanded disclosures regarding fair value measurements. Fair value is defined as the proceeds that would be received for an asset or the exit price that would be paid to transfer a liability in the principal or most advantageous market in an orderly transaction between market participants on the measurement date.

All fair value measurements are classified in the three-tier fair value hierarchy, which categorizes the inputs used in measuring fair value. These categories include (in descending order of priority) Level 1, defined as observable inputs, such as quoted prices in active markets for identical securities; Level 2, defined as inputs other than quoted prices included in Level 1 that are either directly or indirectly observable; and Level 3, defined as significant unobservable inputs in which little or no market data exists, therefore, requiring an entity to develop its own assumptions.

5. Leases

On January 1, 2019, the Company adopted ASC 842 using the modified retrospective transition approach allowed under ASU 2018-11 which releases companies from presenting comparative periods and related disclosures under ASC 842 and requires a cumulative-effect adjustment to the opening balance of retained earnings in the period of adoption (Note 2). The Company is party to two operating leases for office or laboratory space. The Company's finance leases are immaterial both individually and in the aggregate. The Company has elected to apply the short-term lease exception to all leases of one year or less. Rent expense for years ended December 31, 2019, 2018 and 2017 was $278,603, $263,518 and $242,263, respectively, which are included in operating expenses.

Further, the Company has applied the guidance in ASC 842 to its corporate office and laboratory leases and has determined that these should be classified as operating leases. Consequently, as a result of the adoption of ASC 842, the Company recognized a ROU lease asset of approximately $329,384 with a corresponding lease liability of approximately $348,040 based on the present value of the minimum rental payments of such leases. In accordance with ASC 842, the beginning balance of the ROU lease asset was reduced by the existing deferred rent liability at inception of approximately $18,656. In the consolidated balance sheets at December 31, 2019, the Company has a ROU asset balance of $521,392 and a current and non-current lease liability of $242,329 and $302,621, respectively, relating to the ROU lease asset. The balance of both the ROU lease asset and the lease liabilities primarily consists of future payments under the Company's office lease in Boston, Massachusetts.

The Company is party to an operating lease in Boston, Massachusetts for office and laboratory space. The lease commenced in November 2016 with the initial term set to expire in December 2021. This office lease does not have any renewal options.

The Company was party to an operating lease in Solna, Sweden that had month-to-month payments and expired on June 30, 2019. Additionally, the Company entered into a new operating lease for office and laboratory space in Solna, Sweden that is effective July 1, 2019 and expires in June 2022. Base rent for this lease is approximately $128,000 annually. The Company recognized a ROU lease asset of approximately $355,330 with a corresponding lease liability of the same amount based on the present value of the minimum rental payments of such leases.

Aprea Therapeutics, Inc.
Notes to Consolidated Financial Statements (continued)

Quantitative information regarding the Company's leases for the year ended December 31, 2019 is as follows:

Lease Cost	Year Ended December 31, 2019
Operating lease cost	$ 161,856
Other Information	
Operating cash flows paid for amounts included in the measurement of lease liabilities	$ 174,846
Operating lease liabilities arising from obtaining right-of-use assets	$ 355,330
Weighted average remaining lease term (years)	2.0 -2.5
Weighted average discount rate	3.0% - 4.3%

Future lease payments under noncancelable leases are as follows at December 31, 2019:

Future Lease Payments	Operating Leases
2020	$ 251,008
2021	253,303
2022	63,539
Total Lease Payments	$ 567,850
Less: Imputed Interest	(22,900)
Total Lease Liabilities	$ 544,950

As most of the Company's leases do not provide an implicit rate, the Company used its incremental borrowing rate based on the information available at commencement date in determining the present value of lease payments. The Company uses the incremental borrowing rate on January 1, 2019 for operating leases that commenced prior to that date.

6. Accrued expenses

Accrued expenses at consist of the following:

	December 31, 2019	December 31, 2018
Professional fees	$ 207,917	$ 80,771
Compensation and benefits	961,790	624,298
Research and development	4,992,311	2,178,086
Other	480,535	245,617
Total accrued expenses	$ 6,642,553	$ 3,128,772

7. Income taxes

Components of the net loss consist of the following:

	Year ended December 31, 2019	2018	2017
Foreign	$ (25,268,373)	$ (15,713,032)	$ (15,185,931)
Domestic	(2,791,434)	184,763	(4,319)
Net loss	$ (28,059,807)	$ (15,528,269)	$ (15,190,250)

Aprea Therapeutics, Inc.
Notes to Consolidated Financial Statements (continued)

A reconciliation of the effect of applying the federal statutory rate to the net loss and the effective income tax rate:

	Year ended December 31,		
	2019	2018	2017
Statutory federal income tax rate	21.0 %	21.0 %	34.0 %
Earnings in jurisdictions taxed at rates different from the statutory U.S. federal tax rate	0.4 %	1.0 %	(12.0)%
Permanent differences	3.7 %	0.4 %	(0.1)%
Changes in valuation allowance	(25.1)%	(16.7)%	(21.5)%
Rate change due to TCJA	— %	— %	(0.4)%
Rate change due to Swedish tax reform	— %	(5.7)%	— %
Effective income tax rate	— %	— %	— %

Significant components of the Company's deferred taxes as of December 31, 2019 and 2018 are as follows:

	December 31,	
	2019	2018
Deferred tax assets:		
Net operating loss carryforward	$ 20,536,344	$ 12,816,395
Capitalized research and development	—	1,951
Intangible assets	26,842	—
Accrued expenses	17,779	—
Lease liability - ASC 842	128,337	—
Gross deferred tax assets	20,709,302	12,818,346
Valuation allowance	(19,676,794)	(12,661,874)
Total deferred tax assets	1,032,508	156,472
Deferred tax liabilities:		
Fixed assets	(1,692)	(2,050)
Stock Compensation	(908,322)	(154,422)
Right of Use Asset - ASC 842	(122,494)	—
Total deferred tax liabilities	(1,032,508)	(156,472)
Net deferred tax assets (liabilities)	$ —	$ —

The Company has no income tax expense due to operating losses incurred for the years ended December 31, 2019, 2018 and 2017, respectively. The Company has provided a valuation allowance for the full amount of the net deferred tax assets as, based on all available evidence, it is considered more likely than not that all the recorded deferred tax assets will not be realized in a future period. At December 31, 2019, the Company has $89.9 million, $7.3 million and $5.8 million of foreign, federal and state net operating loss carryforwards, respectively, that expire at various dates through 2037. Certain of these foreign, federal and state net operating loss carryforwards may be subject to Internal Revenue Code Section 382 or similar provisions, which impose limitations on their utilization.

The valuation allowance increased in 2019 and 2018 by $7.0 million and $2.5 million, respectively due to the increase in the deferred tax assets by the same amounts; primarily due to net operating loss carryforwards. Realization of the future tax benefits is dependent on many factors, including the Company's ability to generate taxable income within the net operating loss carryforward period. Under the provisions of the U.S. Internal Revenue Code and Sweden tax law, certain changes in the Company's ownership, including a sale of the Company or significant changes in ownership due to sales of equity, may have limited, or may limit in the future, the amount of net operating loss carryforwards that could be used annually to offset future taxable income. For U.S. and Swedish income tax purposes, the Company has not completed a study to assess whether a change of control has occurred or whether there have been changes of control since the Company's formation due to the complexity and cost associated with such study and because there could be additional changes in control in the future. As a result, the Company is not able to estimate the effect of the change in control, if any, on the Company's ability to utilize U.S. or Swedish net operating losses or other tax attribute carryforwards in the

future. For Swedish income tax purposes, the Company's net operating losses may be subject to limitations in accordance with the country's group contribution restriction laws.

The Company files tax returns in Sweden, the United States and Massachusetts, and all tax years since inception remain open to examination by the major taxing jurisdictions to which the Company is subject, as carryforward attributes generated in years past may still be adjusted upon examination by the Internal Revenue Service (IRS) or other authorities if they have or will be used in a future period. The Company is not currently under examination by the IRS or any other jurisdictions for any tax years.

As of December 31, 2019, the Company had no uncertain tax positions. The Company has elected to recognize interest and penalties related to income tax matters as a component of income tax expense, of which no interest or penalties were recorded for the years ended December 31, 2019, 2018 and 2017.

In June 2018, Sweden promulgated changes to the Swedish regulations on corporate income taxation. The law will apply from January 1, 2019. Among other things, the changes decrease the corporate income tax rate in two steps from 22% to 21.4% as of January 1, 2019 and 20.6% as of January 1, 2020. U.S. GAAP requires companies to revalue their deferred tax assets and deferred tax liabilities as of the date of enactment, with the resulting tax effects accounted for in the reporting period of enactment. This revaluation resulted in an overall reduction of deferred taxes of $0.7 million and a corresponding reduction in the valuation allowance. As such, there was no net impact to the Company's statement of operations as a result of the reduction in tax rates.

In December 2017, what is commonly known as the Tax Cuts and Jobs Act (the Tax Act), was signed into law. Among other things, the Tax Act permanently lowers the corporate federal income tax rate to 21% from the statutory rate of 35%, effective for tax years including or commencing January 1, 2018. As a result of the reduction of the corporate federal income tax rate to 21%, U.S. GAAP requires companies to revalue their deferred tax assets and deferred tax liabilities as of the date of enactment, with the resulting tax effects accounted for in the reporting period of enactment. This revaluation resulted in an overall reduction of deferred taxes of $0.1 million and a corresponding reduction in the valuation allowance. As such, there was no net impact to the Company's statement of operations as a result of the reduction in tax rates.

8. Convertible preferred stock

The Company has 440,000,000 shares authorized for all classes of equity combined.

Series A Preferred

In June 2011, the Company issued 145,469 shares of Series A Preferred for gross proceeds of $3,233,417. In March 2016, the Company issued 466,977 shares of Series A Preferred as settlement of its outstanding bridge loans totaling $3,249,627. All 612,446 shares of Series A Preferred were issued to related parties.

In connection with the completion of the Company's IPO in October 2019 (see Note 9), all outstanding shares of Series A Preferred stock were converted to common stock.

Prior to its conversion to common stock, the rights and preferences of the Series A Preferred were as follows:

Conversion—Each share of Series A Preferred may be converted at any time, at the option of the holder, into a share of common stock. The Series A Preferred automatically converts into shares of common stock when 1) shareholders representing a majority of the outstanding preferred shares calls for such conversion or 2) at the closing of an initial public offering of the Company's common stock at a per share price of at least one and a half (1.5) times the average amount (EUR 16.05 based on all Series C preferred shares issued as of December 31, 2018) paid per Series C preferred share (as adjusted for share splits and similar) and aggregate proceeds in excess of EUR 50,000,000.

Dividends—Holders of Series A Preferred do not accrue dividends.

Voting rights—Preferred Stock and common stock vote together as one class on an as converted basis. Common stock voting rights on certain matters are subject to the powers, preferences, and rights of the Preferred Stock. Holders are entitled to vote on all matters and shall have the number of votes equal to the number of shares of common stock into which the shares of Preferred Stock held by such holder are then convertible.

Series B Preferred

In March 2016, the Company issued 3,322,762 shares of Series B Preferred for gross proceeds of $22,609,485. The Company also issued 590,445 shares of Series B Preferred in settlement of its outstanding bridge loans totaling $4,108,818. In October 2017, the Company issued 3,322,762 Series B preferred shares at a price per share of $7.02, for an aggregate purchase price of $23,349,617. All 7,235,969 shares of Series B Preferred were issued to related parties.

In connection with the completion of the Company's IPO in October 2019 (see Note 9), all outstanding shares of Series B Preferred stock were converted to common stock.

Prior to its conversion to common stock, the rights and preferences of the Series B Preferred were as follows:

Conversion—Each share of Series B Preferred may be converted at any time, at the option of the holder, into a share of common stock. The Series B Preferred automatically converts into shares of common stock when 1) shareholders representing a majority of the outstanding preferred shares calls for such conversion or 2) at the closing of an initial public offering of the Company's common stock at a per share price of at least one and a half (1.5) times the average amount (EUR 16.05 based on all Series C preferred shares issued as of December 31, 2018) paid per Series C preferred share (as adjusted for share splits and similar) and aggregate proceeds in excess of EUR 50,000,000.

Dividends—Holders are entitled to dividends of 8%, compounded annually if not paid. No dividends have been declared or paid . The Company has not accrued dividends on the Series B Preferred since dividends are only payable upon the occurrence of a liquidation event, including the transfer of more than fifty percent of the Company's outstanding shares or the transfer of substantially all of the Company's intellectual property. Approximately $8,806,426 of accrued dividends that were payable through December 31, 2018 was added to the stated liquidation preference amount of the Series B Preferred, which totaled $58,874,347 at December 31, 2018.

Voting rights—Preferred Stock and common stock vote together as one class on an as converted basis. Common stock voting rights on certain matters are subject to the powers, preferences, and rights of the Preferred Stock. Holders are entitled to vote on all matters and shall have the number of votes equal to the number of shares of common stock into which the shares of Preferred Stock held by such holder are then convertible.

Series C Preferred

In November 2018, the Company issued 4,712,698 shares of Series C Preferred for gross proceeds of $56,725,342. In February 2019, the Company issued 467,173 shares of Series C Preferred for gross proceeds of $5,651,872. A total of 4,219,854 shares of Series C Preferred were issued to related parties.

In connection with the completion of the Company's IPO in October 2019 (see Note 9), all outstanding shares of Series C Preferred stock were converted to common stock.

Prior to its conversion to common stock, the rights and preferences of the Series C Preferred were as follows:

Conversion—Each share of Series C Preferred may be converted at any time, at the option of the holder, into a share of common stock. The Series C Preferred automatically converts into shares of common stock when 1) shareholders representing a majority of the outstanding preferred shares calls for such conversion or 2) at the closing of an initial public offering of the Company's common stock at a per share price of at least one and a half (1.5) times the average amount (EUR 16.05 based on all Series C preferred shares issued as of December 31, 2018) paid per Series C preferred share (as adjusted for share splits and similar) and aggregate proceeds in excess of EUR 50,000,000.

Dividends—Holders are entitled to dividends of 8%, compounded annually if not paid. No dividends have been declared or paid as of December 31, 2018. The company has not accrued dividends on the Series C Preferred since dividends are only payable upon the occurrence of a liquidation event, including the transfer of more than fifty percent of the Company's outstanding shares or the transfer of substantially all of the Company's intellectual property. Approximately $389,970 of accrued dividends that were payable through December 31, 2018 was added to the stated liquidation preference amount of the Series C Preferred, which totaled $57,115,312 at December 31, 2018.

Voting rights—Preferred Stock and common stock vote together as one class on an as converted basis. Common stock voting rights on certain matters are subject to the powers, preferences, and rights of the Preferred Stock. Holders are entitled to vote on all matters and shall have the number of votes equal to the number of shares of common stock into which the shares of Preferred Stock held by such holder are then convertible.

Liquidation preference

Upon liquidation, dissolution, or winding up of business, the Preferred Stock holders are entitled to receive a liquidation preference in priority to holders of common stock at the original issue price plus, in the case of Series B and Series C Preferred, any unpaid accumulated dividends as follows:

1) If a liquidation event occurs prior to the Company achieving a certain clinical milestone, Series C Preferred shareholders shall receive an amount per Series C Preferred share equal to the original subscription price per Series C Preferred share (as adjusted for share splits and similar) plus unpaid accumulated dividends. Secondly, after the Series C Preferred shareholders have received full payment, the Series B Preferred shareholders shall receive an amount per Series B preferred share equal to the original subscription price per Series B Preferred share (as adjusted for share splits and similar) plus unpaid accumulated dividends. Thirdly, after the Series B and C Preferred shareholders have received full payment, the Series A Preferred shareholders shall receive an amount per Series A preferred share equal to the original subscription price per Series A Preferred share (as adjusted for share splits and similar). When the Preferred A, B and C shareholders are satisfied in full, any excess assets available for distribution will be allocated ratably among holders of common stock and preferred stock based on their pro rata shareholdings on an as-if-converted basis.

2) If a liquidation event occurs after the Company achieves a certain clinical milestone, Series B and C Preferred shareholders, based on their pro rata shareholdings, shall receive an amount per Series B and C Preferred share equal to the original subscription price per Series B and C Preferred share (as adjusted for share splits and similar) plus unpaid accumulated dividends. Secondly, after the Series B and C Preferred shareholders have received full payment, the Series A Preferred shareholders shall receive an amount per Series A preferred share equal to the original subscription price per Series A Preferred share (as adjusted for share splits and similar). When the Preferred A, B and C shareholders are satisfied in full, any excess assets available for distribution will be allocated ratably among holders of common stock and preferred stock based on their pro rata shareholdings on an as-if-converted basis.

The liquidation preferences apply to each series of preferred stock only to the extent the holders would receive less than three times their respective original purchase prices.

9. Common stock

In October 2019, the Company completed its IPO of 6,516,667 shares of common stock at a price to the public of $15.00 per share, which included the exercise in full by the underwriters of their option to purchase an additional 850,000 shares of common stock. The Company received net proceeds of approximately $86.6 million, after deducting underwriting discounts and commissions and other offering expenses.

The Company has 21,022,752 shares of common stock outstanding as of December 31, 2019.

The holders of common stock are entitled to one vote for each share of common stock. In the event of any voluntary or involuntary liquidation, dissolution or winding up of the Company, after the payment or provision for payment of all

debts and liabilities of the Company, the holders of common stock shall be entitled to share in the remaining assets of the Company available for distribution, if any.

10. Stock option plans

In October 2016, the Board of Directors adopted the 2016 Amended and Restated Stock Option Program (the " 2016 Plan"), which provided for the grant of stock options to the Company's employees, officers, directors, and outside consultants for the purchase of up to 1,224,824 shares of the Company's common stock. During 2017, the 2016 Plan was amended to provide up to 1,946,849 shares of the Company's common stock. During 2018, the 2016 Plan was further amended to provide up to 3,069,999 shares of the Company's common stock. Holders of stock options shall be entitled to exercise the vested portion of the stock option provided that a trade sale, as defined in the plan, or initial public offering has occurred. The holders of stock options may also exercise the vested portion of the stock option within six months of termination of employment. Stock options generally vested over a four-year period and were scheduled to expire in October 2026.

In September 2019, the Company's Board of Directors approved the 2019 Equity Incentive Plan (the "2019 Plan) and each outstanding option to purchase Aprea AB ordinary shares pursuant to the 2016 Plan was cancelled and the Company issued to each holder of such Aprea AB option, a substitute option to purchase, on the same terms and conditions as were applicable to such Aprea AB option, shares of the Company's common stock pursuant to the 2019 Plan. As of December 31, 2019, there are no outstanding options under the 2016 Plan.

The Board of Directors has the discretion to provide for accelerated vesting under the 2019 Plan. At December 31, 2019, there were 1,175,494 shares available for future grant under the 2019 Plan.

The Company recorded stock-based compensation expense of $1,345,722, $329,814 and $395,440 during the years ended December 31, 2019, 2018 and 2017, respectively. As of December 31, 2019, there was $10,811,939 of unrecognized compensation cost related to nonvested share-based compensation arrangements granted under the 2019 Plan, which is expected to be recognized over a weighted-average period of approximately 3.6 years.

The fair value of each option award is estimated on the date of grant using Black-Scholes, with the assumptions noted in the table below. Expected volatility for the Company's common stock was determined based on an average of the historical volatility of a peer group of similar public companies. The expected term of options granted to employees was calculated using the simplified method, which represents the average of the contractual term of the option and the weighted-average vesting period of the option. The Company uses the simplified method because it does not have sufficient historical option exercise data to provide a reasonable basis upon which to estimate expected term. The contractual life of the option was used for the expected life of options granted to non-employee. The assumed dividend yield is based upon the Company's expectation of not paying dividends in the foreseeable future. The risk-free rate for periods within the expected life of the option is based upon the Swedish Government Bond Rate in effect at the time of grant.

In determining the exercise prices for options granted, the Company's Board of Directors has considered the fair value of the common stock as of the measurement date. The fair value of the common stock at each award grant date was based upon a variety of factors, including the results obtained from an independent third-party valuation, the Company's financial position and historical financial performance, the status of technological developments within the Company's proposed products, an evaluation or benchmark of the Company's competition, the current business climate in the marketplace, the illiquid nature of the common stock, arm's length sales of the Company's capital stock, including Preferred Stock, the effect of the rights and preferences of the preferred shareholders, and the prospects of a liquidity event, among others.

Aprea Therapeutics, Inc.
Notes to Consolidated Financial Statements (continued)

The assumptions used in Black-Scholes are as follows:

	Year ended December 31,		
	2019	2018	2017
Expected volatility	73.5% - 74.5%	71.5 %	71.9% - 75.4%
Risk-free rate	1.53% - 2.63%	2.9 %	2.3% - 2.5%
Expected dividend yield	0%	0 %	0%
Expected term in years	6.08 - 7.59	8.2	8.6 - 9.7

A summary of option activity under the Plan during the years ended December 31, 2019, 2018 and 2017 are as follows:

	Number of options	Weighted-average exercise price per share	Weighted average remaining contractual term (in years)	Aggregate intrinsic value
Outstanding at January 1, 2017	1,237,292	$ 1.85	9.2	
Granted	663,224	0.73		
Exercised	—	—		
Cancelled/Forfeited	(3,310)	0.92		
Outstanding at December 31, 2017	1,897,206	$ 1.46	8.3	
Granted	24,067	1.01		
Exercised	(2,306)	0.92		
Cancelled/Forfeited	(74,779)	17.31		
Outstanding at December 31, 2018	1,844,188	$ 0.82	7.6	
Granted	2,018,796	8.82		
Exercised	(322,267)	0.23		
Cancelled/Forfeited	(40,783)	0.99		
Outstanding at December 31, 2019	3,499,934	$ 5.49	7.5	$ 141,413,705
Exercisable at December 31, 2019	1,203,298	$ 0.93	6.7	$ 54,101,434
Vested or expected to vest at December 31, 2019	3,499,934	$ 5.49	7.5	$ 141,413,705

The weighted-average grant date fair value of options granted during the years ended December 31, 2019, 2018 and 2017, was $6.68, $0.69 and $0.75 per share, respectively.

11. Commitments and contingencies

The Company records a provision for contingent losses when it is both probable that a liability has been incurred and the amount of the loss can be reasonably estimated. As of December 31, 2019, the Company has not recorded a provision for any contingent losses.

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

None.

Item 9A. Controls and Procedures

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 of December 31, 2019. The term "disclosure controls and procedures," as defined in Rules 13a-15(e) and 15d-15(e) under the Exchange Act, mean controls and other procedures of a company that are designed to ensure that information required to be disclosed by us in the reports that we file or submit under the Exchange Act is recorded, processed, summarized and reported within the time periods specified in the SEC's rules and forms. Disclosure controls include, without limitation, controls and procedures designed to ensure that information required to be disclosed by a company in the reports that it files or submits under the Exchange Act is accumulated and communicated to management, including our principal executive and principal financial officers, as appropriate to allow timely decisions regarding required disclosure. Management recognizes that any controls and procedures, no matter how well designed and operated, can provide only reasonable assurance of achieving their objectives and management necessarily applies its judgment in evaluating the cost-benefit relationship of possible controls and procedures. Based on the evaluation of our disclosure controls and procedures as of December 31, 2019, our chief executive officer and chief financial officer concluded that, as of such date, our disclosure controls and procedures were effective at the reasonable level.

Management’s Annual Report on Internal Controls Over Financial Reporting

This Annual Report on Form 10-K does not include a report of management’s assessment regarding internal control over financial reporting or an attestation report of our independent registered public accounting firm due to a transition period established by rules of the Securities and Exchange Commission for newly public companies.

Changes in Internal Control Over Financial Reporting

Other than the remediation of our previously disclosed material weakness that related to our internal control infrastructure as of December 31, 2018 and 2017, there were no changes in our internal control over financial reporting that occurred during the period covered by this Annual Report that has 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 will be included in an amendment to this Annual Report on Form 10-K or incorporated by reference from our definitive proxy statement to be filed pursuant to Rule 14A.

Item 11. Executive Compensation

The information required by this item will be included in an amendment to this Annual Report on Form 10-K or incorporated by reference from our definitive proxy statement to be filed pursuant to Rule 14A.

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

The information required by this item will be included in an amendment to this Annual Report on Form 10-K or incorporated by reference from our definitive proxy statement to be filed pursuant to Rule 14A.

Item 13. Certain Relationships and Related Transactions and Director Independence

The information required by this item will be included in an amendment to this Annual Report on Form 10-K or incorporated by reference from our definitive proxy statement to be filed pursuant to Rule 14A.

Item 14. Principal Accounting Fees and Services

The information required by this item will be included in an amendment to this Annual Report on Form 10-K or incorporated by reference from our definitive proxy statement to be filed pursuant to Rule 14A.

PART IV

Item 15. Exhibits, Financial Statement Schedules

The following documents are filed as part of this Annual Report on Form 10-K:

(a) Financial Statements

The information concerning our consolidated financial statements, and Report of Independent Registered Public Accounting Firm required by this Item is incorporated by reference herein to the section of this Annual Report on Form 10-K in Item 8, entitled "Financial Statements and Supplementary Data."

(b) Financial Statement Schedules

All schedules have been omitted because the required information is not present or not present in amounts sufficient to require submission of the schedules, or because the information required is included in the Financial Statements or notes thereto.

(c) Exhibits

The list of exhibits filed with this report is set forth in the Exhibit Index immediately preceding the signature page and is incorporated herein by reference.

Exhibit Number	Description of Document
3.1##	Amended and Restated Certificate of Incorporation of the Registrant (incorporated by reference to Exhibit 3.1 to the Current Report on Form 8-K filed on October 7, 2019)
3.2##	Amended and Restated Bylaws of the Registrant (incorporated by reference to Exhibit 3.2 to the Current Report on Form 8-K filed on October 7, 2019)
4.1	Description of the Company's Common Stock, $0.001 par value
10.1##+	Form of 2019 Stock Incentive Plan and form of agreements thereunder (incorporated by reference to Exhibit 10.1 to the Registration Statement on Form S-1 (File No. 333-233662)).
10.2##+	Form of 2019 Employee Stock Purchase Plan (incorporated by reference to Exhibit 10.2 to the Registration Statement on Form S-1 (File No. 333-233662))
10.3##†	Service Agreement, between Aprea AB and Syngene International Private Limited (incorporated by reference to Exhibit 10.3 to the Registration Statement on Form S-1 (File No. 333-233662))
10.4##	Amended and Restated Registration Rights Agreement by and among the Registrant and the shareholders party thereto (incorporated by reference to Exhibit 10.4 to the Registration Statement on Form S-1 (File No. 333-233662))
10.5##+	Form of Indemnification Agreement between the Registrant and each of its directors and executive officers (incorporated by reference to Exhibit 10.5 to the Registration Statement on Form S-1 (File No. 333-233662))
10.6##+	Employment Agreement between the Registrant and Christian S. Schade (incorporated by reference to Exhibit 10.6 to the Registration Statement on Form S-1 (File No. 333-233662))

Exhibit Number	Description of Document
10.7##+	Form of Executive Employment Agreement (incorporated by reference to Exhibit 10.7 to the Registration Statement on Form S-1 (File No. 333-233662))
10.8##+	Employment Agreement between the Registrant and Lars Abrahmsen, Ph.D. (incorporated by reference to Exhibit 10.8 to the Registration Statement on Form S-1 (File No. 333-233662))
10.9##+	Employment Agreement between the Registrant and Gregory A. Korbel, Ph.D. (incorporated by reference to Exhibit 10.9 to the Registration Statement on Form S-1 (File No. 333-233662))
10.10##+	Employment Agreement between the Registrant and Scott M. Coiante (incorporated by reference to Exhibit 10.10 to the Registration Statement on Form S-1 (File No. 333-233662))
10.11##†	Master Manufacturing and Supply Agreement, between Aprea Therapeutics AB and Siegfried Hameln GmbH (incorporated by reference to Exhibit 10.11 to the Registration Statement on Form S-1 (File No. 333-233662))
23.1	Consent of Independent Registered Public Accounting Firm
23.2	Consent of Independent Registered Public Accounting Firm
31.1	Certification of the Registrant's Chief Executive Officer pursuant to Section 302 of the Sarbanes-Oxley Act of 2002.
31.2	Certification of the Registrant's Chief Financial Officer pursuant to Section 302 of the Sarbanes-Oxley Act of 2002.
32.1*	Certification of the Registrant's Chief Executive Officer pursuant to Section 906 of the Sarbanes-Oxley Act of 2002.
32.2*	Certification of the Registrant's Chief Financial Officer pursuant to Section 906 of the Sarbanes-Oxley Act of 2002.
101.INS	XBRL Instance Taxonomy
101.SCH	XBRL Taxonomy Extension Schema Document
101.CAL	XBRL Taxonomy Extension Calculation Linkbase Document
101.DEF	XBRL Taxonomy Extension Definition Linkbase Document
101.LAB	XBRL Taxonomy Extension Labels Linkbase Document
101.PRE	XBRL Taxonomy Extension Presentation Linkbase Document

Previously filed.

+ Indicates a management contract or compensatory plan.

† Portions of this exhibit (indicated by bracketed asterisks) have been omitted as the Company has determined that (i) the omitted information is not material and (ii) the omitted information would likely cause competitive harm to the Company if publicly disclosed.

* The certifications furnished in Exhibit 32.1 and Exhibit 32.2 hereto are deemed to accompany this Quarterly Report and will not be deemed "filed" for purposes of Section 18 of the Securities Exchange Act of 1934, as amended, except to the extent that the registrant specifically incorporates it by reference.

Item 16. Form 10-K Summary

None.

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, on March 27, 2020.

APREA THERAPEUTICS, INC.

By /s/ CHRISTIAN S. SCHADE
Christian S. Schade
President and Chief 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 in the capacities and on the dates indicated.

Signature	Title	Date
/s/ CHRISTIAN S. SCHADE Christian S. Schade	Chief Executive Officer and Director (Principal Executive Officer)	March 27, 2020
/s/ SCOTT M. COIANTE Scott M. Coiante	Chief Financial Officer (Principal Financial and Accounting Officer)	March 27, 2020
/s/ SCOTT M. ROCKLAGE, Ph.D. Scott M. Rocklage, Ph.D.	Chairman of the Board of Directors	March 27, 2020
/s/ JOHAN CHRISTENSON, M.D., Ph.D. Johan Christenson, M.D., Ph.D.	Director	March 27, 2020
/s/ JOHN B. HENNEMAN, III John B. Henneman, III	Director	March 27, 2020
/s/ JONATHAN HEPPLE, Ph.D. Jonathan Hepple, Ph.D.	Director	March 27, 2020
/s/ GUIDO MAGNI, M.D., Ph.D. Guido Magni, M.D., Ph.D.	Director	March 27, 2020
/s/ BERND R. SEIZINGER, M.D., Ph.D. Bernd R. Seizinger, M.D., Ph.D.	Director	March 27, 2020

DESCRIPTION OF REGISTRANT'S SECURITIES REGISTERED PURSUANT TO SECTION 12 OF THE SECURITIES EXCHANGE ACT OF 1934

Aprea Therapeutics, Inc. has one class of securities registered under Section 12 of the Securities Exchange Act of 1934, as amended (the "Exchange Act"): its common stock, par value $0.001 per share (the "common stock"). For purposes of this exhibit, unless the context otherwise requires, the words "we," "our," "us" and "our company" refer to Aprea Therapeutics, Inc., a Delaware corporation.

Description of Common Stock

General

The following summary sets forth some of the general terms of our common stock. Because this is a summary, it does not contain all of the information that may be important to you. For a more detailed description of our common stock, you should read our amended and restated certificate of incorporation and the amended and restated bylaws, each of which is an exhibit to our Annual Report on Form 10-K to which this summary is also an exhibit, and the applicable provisions of the Delaware General Corporation Law (the "DGCL").

Our charter authorizes us to issue up to 400,000,000 shares of common stock, $0.001 par value per share and 40,000,000 shares of preferred stock, par value $0.001 per share.

Voting Rights

Holders of our common stock are entitled to one vote for each share held on all matters submitted to a vote of stockholders and do not have cumulative voting rights. An election of directors by our stockholders will be determined by a plurality of the votes cast by the stockholders entitled to vote on the election. Other matters shall be decided by the affirmative vote of our stockholders having a majority in voting power of the votes cast by the stockholders present or represented and voting on such matter, except as otherwise disclosed below.

Dividends

Holders of common stock are entitled to receive proportionately any dividends as may be declared by our board of directors, subject to any preferential dividend rights of outstanding preferred stock.

Liquidation

In the event of our liquidation or dissolution, the holders of common stock are entitled to receive proportionately all assets available for distribution to stockholders after the payment of all debts and other liabilities and subject to the prior rights of any outstanding preferred stock.

Rights and Preferences

Holders of common stock have no preemptive, subscription, redemption or conversion rights. The rights, preferences and privileges of holders of common stock are subject to and may be adversely affected by the rights of the holders of shares of any series of preferred stock that we may designate and issue in the future.

Preferred stock

Our board of directors is authorized to issue shares of preferred stock in one or more series without stockholder approval. Our board of directors has the discretion to determine the rights, preferences, privileges and restrictions, including voting rights, dividend rights, conversion rights, redemption privileges and liquidation preferences, of each series of preferred stock.

The purpose of authorizing our board of directors to issue preferred stock and determine its rights and preferences is to eliminate delays associated with a stockholder vote on specific issuances. The issuance of preferred stock, while providing flexibility in connection with possible acquisitions, future financings and other corporate purposes, could have the effect of making it more difficult for a third party to acquire, or could discourage a third party from seeking to acquire, a majority of our outstanding voting stock.

Anti-Takeover effects of Delaware law and our charter and bylaws

Delaware law, our certificate of incorporation and our bylaws contain provisions that could have the effect of delaying, deferring or discouraging another party from acquiring control of us. These provisions, which are summarized below, are expected to discourage coercive takeover practices and inadequate takeover bids. These provisions are also designed to encourage persons seeking to acquire control of us to first negotiate with our board of directors.

Staggered board; removal of directors

Our certificate of incorporation and bylaws divides our board of directors into three classes with staggered three-year terms. In addition, a director may only be removed for cause and only by the affirmative vote of the holders of at least 75% of the votes that all of our stockholders would be entitled to cast in an annual election of directors. Any vacancy on our board of directors, including a vacancy resulting from an enlargement of our board of directors, will only be able to be filled by vote of a majority of our directors then in office. The classification of our board of directors and the limitations on the removal of directors and filling of vacancies could make it more difficult for a third party to acquire, or discourage a third party from seeking to acquire, control of our company.

Stockholder action by written consent; special meetings

Our certificate of incorporation provides that any action required or permitted to be taken by our stockholders must be effected at a duly called annual or special meeting of such holders and may not be effected by any consent in writing by such holders. Our certificate of incorporation and bylaws also provide that, except as otherwise required by law, special meetings of our stockholders can only be called by our chairman of the board, our Chief Executive Officer or our board of directors.

Advance notice requirements for stockholder proposals

Our bylaws establish an advance notice procedure for stockholder proposals to be brought before an annual meeting of stockholders, including proposed nominations of persons for election to our board of directors. Stockholders at an annual meeting are only able to consider proposals or nominations specified in the notice of meeting or brought before the meeting by or at the direction of our board of directors or by a stockholder of record on the record date for the meeting who is entitled to vote at the meeting and who has delivered timely written notice in proper form to our secretary of the stockholder’s intention to bring such business before the meeting. These provisions could have the effect of delaying until the next stockholder meeting stockholder actions that are favored by the holders of a majority of our outstanding voting securities.

Delaware business combination statute

We are subject to Section 203 of the DGCL. Subject to certain exceptions, Section 203 prevents a publicly held Delaware corporation from engaging in a “business combination” with any “interested stockholder” for three years following the date that the person became an interested stockholder, unless the interested stockholder attained such status with the approval of our board of directors or unless the business combination is approved in a prescribed manner. A “business combination” includes, among other things, a merger or consolidation involving us and the “interested stockholder” and the sale of more than 10% of our assets. In general, an “interested stockholder” is any entity or person beneficially owning 15% or more of our outstanding voting stock and any entity or person affiliated with or controlling or controlled by such entity or person.

Amendment of certificate of incorporation and bylaws

DGCL provides generally that the affirmative vote of a majority of the shares entitled to vote on any matter is required to amend a corporation’s certificate of incorporation or bylaws, unless a corporation’s certificate of incorporation or

bylaws, as the case may be, requires a greater percentage. Our bylaws may be amended or repealed by a majority vote of our board of directors or by the affirmative vote of the holders of at least 75% of the votes that all of our stockholders would be entitled to cast in any annual election of directors. In addition, the affirmative vote of the holders of at least 75% of the votes that all of our stockholders would be entitled to cast in any annual election of directors is required to amend or repeal or to adopt any provisions inconsistent with any of the provisions of our certificate of incorporation described above under "Staggered board; removal of directors" and "Stockholder action by written consent; special meetings."

Exclusive forum selection

Our certificate of incorporation provides, unless we consent in writing to the selection of an alternative forum, to the fullest extent permitted by law, the Court of Chancery of the State of Delaware (or if the Court of Chancery does not have jurisdiction, the federal district court for the District of Delaware) shall be the sole and exclusive forum for (1) any derivative action or proceeding brought on behalf of our company under Delaware law, (2) any action asserting a claim of breach of a fiduciary duty owed by any of our directors, officers or employees to our company or our stockholders, (3) any action asserting a claim against our company arising pursuant to any provision of the DGCL or our certificate of incorporation or bylaws, (4) any action asserting a claim against our company governed by the internal affairs doctrine or (5) any other action asserting an "internal corporate claim," as defined in Section 115 of the DGCL. These exclusive-forum provisions do not currently apply to claims under the Securities Act of 1933, as amended, or the Exchange Act. Any person or entity purchasing or otherwise acquiring any interest in our securities shall be deemed to have notice of and consented to this provision. Although we believe these provisions benefit us by providing increased consistency in the application of Delaware law for the specified types of actions and proceedings, the provisions may have the effect of discouraging lawsuits against us or our directors and officers.

Listing on The Nasdaq Global Select Market

Our common stock is listed on The Nasdaq Global Select Market under the symbol "APRE."

Authorized but unissued shares

The authorized but unissued shares of common stock and preferred stock are available for future issuance without stockholder approval, subject to any limitations imposed by the listing requirements of The Nasdaq Global Select Market. These additional shares may be used for a variety of corporate finance transactions, acquisitions and employee benefit plans. The existence of authorized but unissued and unreserved common stock and preferred stock could make it more difficult or discourage an attempt to obtain control of us by means of a proxy contest, tender offer, merger or otherwise.

Transfer agent and registrar

The transfer agent and registrar for our common stock is Computershare Trust Company, N.A. The transfer agent and registrar's address is 150 Royall St., Canton, MA 02021.

Exhibit 23.1

Consent of Independent Registered Public Accounting Firm

We consent to the incorporation by reference in the Registration Statement (Form S-8 No. 333-234765), pertaining to the 2019 Equity Incentive Plan of Aprea Therapeutics, Inc. of our report dated March 27, 2020, with respect to the consolidated financial statements of Aprea Therapeutics, Inc. included in this Annual Report (Form 10-K) for the year ended December 31, 2019.

/s/ Ernst & Young LLP

Iselin, New Jersey
March 27, 2020

Exhibit 23.2

Consent of Independent Registered Public Accounting Firm

We consent to the incorporation by reference in the Registration Statement (Form S-8 No. 333-234765) pertaining to the 2019 Equity Incentive Plan of Aprea Therapeutics, Inc. of our report dated August 20, 2019 (except for the retroactive effect of the 1-for-1.6045 stock split of the Company's common stock as described in Note 2, as to which the date is September 27, 2019), with respect to the consolidated financial statements of Aprea Therapeutics AB included in this Annual Report (Form 10-K) for the year ended December 31, 2019.

/s/ Ernst & Young AB

Stockholm, Sweden
March 27, 2020

Exhibit 31.1

CERTIFICATION OF PERIODIC REPORT
PURSUANT TO SECTION 302 OF THE SARBANES-OXLEY ACT OF 2002

I, Christian S. Schade, certify that:

1. I have reviewed this Annual Report on Form 10-K of Aprea Therapeutics, 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) 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

   c) 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 27, 2020

/s/ Christian S. Schade
Christian S. Schade
Chief Executive Officer
(Principal Executive Officer)

Exhibit 31.2

CERTIFICATION OF PERIODIC REPORT PURSUANT TO SECTION 302 OF THE SARBANES-OXLEY ACT OF 2002

I, Scott M. Coiante, certify that:

1. I have reviewed this Annual Report on Form 10-K of Aprea Therapeutics, 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) 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

   c) 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 27, 2020

/s/ Scott M. Coiante
Scott M. Coiante
Chief Financial Officer
(Principal Financial and Accounting Officer)

Exhibit 32.1

STATEMENT OF CHIEF EXECUTIVE OFFICER OF
APREA THERAPEUTICS, INC.
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 of Aprea Therapeutics, Inc. (the "Company") on Form 10-K for the year ended December 31, 2019 as filed with the Securities and Exchange Commission (the "Report"), I, Christian S. Schade, Chief Executive Officer of the Company, certify, pursuant to 18 U.S.C. §1350, as adopted pursuant to §906 of the Sarbanes-Oxley Act of 2002, that, based on my knowledge:

1) The Report fully complies with the requirements of Section 13(a) or 15(d) of the Securities Exchange Act of 1934, as amended; 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 27, 2020

/s/ Christian S. Schade
Christian S. Schade
Chief Executive Officer
(Principal Executive Officer)

Exhibit 32.2

STATEMENT OF CHIEF ACCOUNTING OFFICER OF
APREA THERAPEUTICS, INC.
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 of Aprea Therapeutics, Inc. (the "Company") on Form 10-K for the year ended December 31, 2019 as filed with the Securities and Exchange Commission (the "Report"), I, Scott M. Coiante, Chief Accounting Officer of the Company, certify, pursuant to 18 U.S.C. §1350, as adopted pursuant to §906 of the Sarbanes-Oxley Act of 2002, that, based on my knowledge:

1) The Report fully complies with the requirements of Section 13(a) or 15(d) of the Securities Exchange Act of 1934, as amended; 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 27, 2020

/s/ Scott M. Coiante
Scott M. Coiante
Chief Financial Officer
(Principal Financial and Accounting Officer)